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On the link between saccadic adaptation and visuospatial attention

Judith Nicolas

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On the link between saccadic adaptation and visuospatial attention

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Abstract

Attention and Saccadic Adaptation (SA) are critical components of visual perception, the former enhancing sensory processing of selected objects, the latter maintaining the eye movements accuracy towards them. Also, a similar dichotomy could be applied to both: voluntary saccades and endogenous attentional shifts follow internal goals while reactive saccades and exogenous shifts are elicited by sudden changes in the environment. Further, their neural substrates partially overlap and they impact each other behaviorally. This PhD work investigates the hypothesis of a functional coupling linking attention and SA in healthy humans.

Our experimental contributions all rely on the measurement of attentional performances before and after an exposure to SA (or control). In the first study, we recorded brain magnetic fields to investigate neurophysiological bases of the reactive/exogenous coupling. In the second study, we compared exogenous orienting measured in a Posner-like paradigm before and after reactive SA. Finally, using the same design, the third experiment investigated the voluntary/endogenous modality. We found that SA boosted the orienting of spatial attention and increased gamma band activity in the reactive/exogenous modality.

We thus propose that the functional coupling between attention and SA relies on neuronal populations co-activated by both oculomotor plasticity and attention in the Posterior Parietal Cortex (PPC). The initial activation would emerge from a dual effect of the cerebellum inhibiting the left PPC and activating the right PPC. This effect would increase the right hemispheric dominance and the leftward attentional bias. This work opens new perspectives for the rehabilitation of visuoattentional deficits.

Keywords: Oculomotor plasticity; Visuospatial attention; Saccades; Functional coupling; Gamma band activity.

Résumé

L'attention et l'Adaptation Saccadique (AS) sont des composants essentiels de la perception visuelle, le premier renforce le traitement sensoriel des items sélectionnés, le second maintient la précision des mouvements des yeux vers ceux-ci. Ils partagent aussi une dichotomie : les saccades volontaires et l'orientation endogène de l'attention suivent nos buts internes tandis que les saccades réactives et l'orientation exogène répondent aux changements soudains dans l'espace visuel. Leurs substrats neuronaux se superposent en partie. Enfin, chacun impacte l'autre au niveau comportemental. Ce travail de doctorat teste l'hypothèse d'un couplage fonctionnel entre attention et AS.

Toutes nos études chez l'humain sain reposent sur la mesure des performances attentionnelles avant et après l'exposition à l'AS (ou contrôle). Dans la première nous avons exploré les bases neurophysiologiques du couplage réactif/exogène en magnétoencéphalographie. Dans la suivante nous avons comparé l'orientation exogène mesurée par un paradigme de Posner avant et après AS réactive. La dernière, basée sur le même modèle, explorait la modalité volontaire/endogène. Nos résultats montrent que l'AS augmente l'activité oscillatoire gamma et renforce l'orientation de l'attention spatiale.

Nous proposons que le couplage repose sur la co-activation de populations neuronales par la plasticité oculomotrice et l'attention au niveau du Cortex Pariétal Postérieur (CPP). Cette activation émerge initialement d'un double effet du cervelet qui inhibe le CPP gauche et active le CPP droit. Cet effet augmente la dominance hémisphérique droite et le biais attentionnel vers la gauche. Notre travail ouvre des perspectives de rééducation des déficits visuo-attentionnels.

Mots-clés: Plasticité oculomotrice, Attention Visuo-spatiale; Saccades; Couplage fonctionnel; Activité oscillatoire Gamma.

Résumé substantiel

Lorsque nous regardons autour de nous, nous avons une impression de percevoir notre environnement visuel de façon claire et limpide. Cependant, notre perception est précise seulement au niveau de la fovéa, le point au centre de notre rétine où l'acuité visuelle est maximale. Ainsi, pour récolter des informations sur les objets qui nous entourent, nous devons déplacer notre regard à l'aide de mouvements des yeux très rapides, appelés saccades. Ces saccades peuvent être induites de deux manières différentes. Les Saccades Volontaires (SV) sont générées selon nos buts internes tandis que les Saccades Réactives (SR) se produisent en réaction à un changement soudain dans l'espace visuel qui nous entoure. La précision des saccades est donc essentielle puisqu'elles permettent une perception accrue des objets au niveau de la fovéa. Le maintien de la précision des saccades tout au long de la vie se fait grâce à des phénomènes de plasticité cérébrale. Lorsqu'une erreur de visée a lieu de manière répétée, la commande motrice envoyée aux muscles extra-oculaires va être modifiée afin de restaurer la correspondance entre le vecteur visuel induisant la saccade et le vecteur moteur produisant la saccade. La plasticité des saccades, aussi appelée Adaptation Saccadique (AS) a été étudiée en laboratoire depuis l'introduction par McLaughlin en 1967 du paradigme de double saut de cible. Ce paradigme consiste à déplacer la cible de la saccade pendant l'exécution de celle-ci. Grâce au phénomène de suppression saccadique, ce saut n'est pas perçu et le système nerveux central interprète ce décalage comme une erreur de visée. L'amplitude de la saccade sera alors progressivement modifiée pour atteindre le point déplacé à l'arrivée de la saccade. Cette modification peut se faire en diminution d'amplitude ou en augmentation d'amplitude. Récemment, Gerardin et al. (2012) ont utilisé ce paradigme en diminution d'amplitude en IRM fonctionnelle et ont montré que l'adaptation des SR module l'activité BOLD au niveau de l'aire MT/V5 et de la jonction temporo-pariétale (TPJ). L'adaptation des SV activait le sillon intrapariétal (IPS). Cette implication d'aires cérébrales dans l'AS vient s'ajouter à l'implication du cervelet décrite depuis plusieurs décennies (voir pour revue Prsa and Thier, 2011).

Les saccades ne sont pas le seul mécanisme pour améliorer la perception visuelle. L'attention visuo-spatiale, accompagnée de mouvement des yeux ou non, permet aussi d'augmenter le traitement sensoriel d'objets qui se trouvent à l'intérieur du focus attentionnel. Une fois encore, ce focus peut être déplacé de deux manières différentes : endogène, suivant nos buts internes ; et exogène, en réaction à un changement dans l'environnement visuel. Ces mouvements endogène ou exogène de l'attention peuvent être mesurés grâce à des variantes spécifiques d'un protocole décrit initialement par Posner (1980).

Les substrats du déplacement endogène de l'attention et ceux de l'adaptation des SV se superposent au niveau de l'IPS et les substrats du déplacement exogène et ceux de l'adaptation des SR se superposent au niveau de la TPJ (Gerardin et al., 2012; Corbetta et al., 2008). Aussi, Gerardin et al. (2015) ont montré que l'augmentation de la charge attentionnelle augmente l'efficacité de l'AS. Enfin, Habchi et al. (2015) ont montré que l'adaptation des SR accélérât la vitesse de traitement de stimuli visuels apparaissant soudainement. Prises ensemble, ces deux études suggèrent, au niveau comportemental, un impact réciproque entre l'attention visuo-spatiale et l'AS.

Le travail de cette thèse est basé sur l'hypothèse principale d'un couplage fonctionnel entre l'attention visuo-spatiale et l'AS. Les hypothèses de travail que nous allons développer dans nos contributions expérimentales sont : (1) l'AS augmente l'excitabilité corticale reflétée par une augmentation de la puissance dans la bande de gamma (oscillations rapides > 35Hz) au niveau de régions cérébrales impliquées dans l'AS et l'attention ; (2) l'adaptation des SR a un effet bénéfique sur l'orientation exogène de l'attention ; (3) l'adaptation des SV a un effet bénéfique sur l'orientation endogène de l'attention.

Concernant notre première hypothèse de travail, nous avons effectué une expérience en magnétoencéphalographie. Les champs magnétiques ainsi que les mouvements des yeux de 12 sujets humains sains étaient enregistrés durant toute la durée du protocole. Chaque sujet a réalisé une session comprenant une exposition à l'adaptation des SR dirigées vers la gauche et une session comprenant une exposition contrôle. Avant et après l'exposition, le temps de réaction à des cibles présentées aléatoirement dans l'espace et dans le temps étaient recueillis. Cette expérience n'a pas mis en évidence l'effet bénéfique attendu de l'AS sur la vitesse de réponse aux cibles visuelles, sur le plan comportemental. Cependant, nous avons pu montrer que l'adaptation des SR induit une augmentation de la puissance dans la bande gamma et ce dans un réseau cérébral incluant le réseau ventral de l'attention exogène.

Concernant notre deuxième hypothèse, nous avons proposé à 18 sujets humains sains un protocole mesurant l'orientation exogène de l'attention grâce à un paradigme de Posner avant et après exposition à l'adaptation des SR dirigées vers la gauche. Chacun des sujets a été soumis à une exposition à l'AS en diminution d'amplitude, à une exposition à l'AS en augmentation d'amplitude et à une exposition contrôle. L'analyse comparative des résultats de ces trois sessions expérimentales a mis en évidence que l'adaptation en diminution d'amplitude des SR vers la gauche, mais pas les deux autres expositions, renforçait l'orientation exogène de l'attention vers les cibles présentées dans l'hémichamp gauche et ce quelle que soit l'excentricité testée (3°, 7°, 11° et 15° d'angle visuel).

Enfin, concernant la troisième hypothèse, nous avons proposé à 18 sujets humains sains un protocole mesurant l'orientation endogène de l'attention grâce à un paradigme de Posner avant et après exposition à l'adaptation en diminution d'amplitude des SV. Chacun des sujets a été soumis à une exposition à l'adaptation des SV vers la gauche, à une exposition à l'adaptation des SV vers la droite et à une exposition contrôle. Cette expérience a mis en évidence que l'adaptation en diminution d'amplitude des SV vers la gauche renforçait l'orientation endogène de l'attention vers les cibles présentées à 3° d'excentricité, et non à 7.5°, dans l'hémichamp gauche et dans l'hémichamp droit.

Ainsi, notre travail montre que l'adaptation des SR augmente l'excitabilité cérébrale dans un réseau recouvrant le réseau ventral de l'attention. Nous faisons l'hypothèse que l'adaptation des SV augmente l'excitabilité cérébrale dans le réseau dorsal de l'attention. Aussi, sur le plan comportemental, notre travail montre que l'AS renforce l'orientation de l'attention mais seulement après adaptation en diminution d'amplitude des saccades vers la gauche (SV et SR).

Nous proposons, sur la base de ces résultats et de la littérature, que le couplage entre attention et AS repose sur la co-activation de populations neuronales par la plasticité oculomotrice et l'attention au niveau du Cortex Pariétal Postérieur (CPP). Cette activation émergerait initialement d'un double effet du cervelet. L'encodage du signal d'erreur induisant l'adaptation en diminution d'amplitude serait soutenu par l'hémisphère droit du cervelet dans le cadre de l'adaptation en diminution d'amplitude des saccades vers la gauche. L'hémisphère droit du cervelet enverrait des signaux inhibiteurs vers l'IPS de

l'hémisphère gauche. Par conséquent, cette inhibition diminuerait l'inhibition inter-hémisphérique que les deux IPS exercent l'un sur l'autre. L'IPS de l'hémisphère droit serait donc moins soumis à l'inhibition de son homologue de l'hémisphère gauche ce qui augmenterait son excitabilité. La direction des saccades adaptées (gauche) serait encodée par l'hémisphère gauche du cervelet. Ce dernier enverrait des signaux d'activation au cortex pariétal droit (TPJ dans le cadre des SR et IPS dans le cadre des SV). Combiné à la diminution de l'inhibition inter-hémisphérique, la sur-activation du PPC de l'hémisphère droit serait d'autant plus forte. L'activation du réseau dorsal et du réseau ventral de l'attention modulerait l'excitabilité cérébrale au niveau des aires sensorielles telles que les cortex visuels. Ainsi, le traitement des stimuli visuels par ces derniers serait plus performant, se reflétant au niveau comportemental par une orientation plus rapide de l'attention.

Outre les apports aux connaissances actuelles sur les liens fonctionnels entre les systèmes saccadique et attentionnel, les découvertes de ce travail de thèse d'un effet bénéfique de l'AS chez les sujets sains permettent d'envisager une application de l'AS à la population des patients. Comme première perspective, nous testons actuellement un protocole de rééducation par l'AS des troubles de l'attention spatiale après accident vasculaire cérébral.

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List of acronyms

EXPANDED FORM	ACRONYMS
Anti-Saccades	AS
Basal Ganglia	BG
Brainstem Burst Generator	BBG
Blood Oxygen Level Dependent	BOLD
Caudate Nucleus	CN
Central Nervous System	CNS
Corollary Discharge	CD
Electro-/Magneto-Encephalogram	EEG/MEG
Event-Related Potentials	ERP
Excitatory/Inhibitory Burst Neurons	EBN/IBN
Extraocular Muscles	EOM
Fixation Point	FP
Fastigial Oculomotor Region	FOR
Frontal Eye Field	FEF
Gamma Band Activity	GBA
Hand Pointing Movements	HPM
Illusory Line Motion	ILM
Inferior Frontal Gyrus	IFG
Inferior Frontal Junction	IFJ
Inferior Olive	IO
Interhemispheric Inhibition	IHI
Intraparietal Sulcus	IPS
Intra-Saccadic Step	ISS
Lateral Geniculate Nucleus	LGN
Lateral Intraparietal	LIP
Magnetic Resonance Imaging	MRI
Medial Dorsal Thalamic Nucleus	MD
Middle Frontal Gyrus	MFG
Neglect Patients	NP
Norepinephrine	NE

Nucleus Reticularis Tegmenti Pontis	NRTP
Oculomotor Vermis	OMV
Omnipause Neurons	OPN
Parietal Eye Field	PEF
Positron Emission Tomography	PET
Posterior Parietal Cortex	PPC
Prefrontal Cortex	PFC
Primary Visual Cortex	V1
Prismatic Adaptation	PA
Reaction Times	RT
Reactive Saccade	RS
Receptive Field	RF
Saccade-Related Burst Neurons	SRBN
Saccadic Adaptation	SA
Single Case Experimental Design	SCED
Short-/Long-Lead Burst Neurons	SLBN/LLBN
Stimulus Onset Asynchrony	SOA
Superior Colliculus	SC
Superior Longitudinal Fasciculus	SLF
Superior Parietal Lobule	SPL
Supplementary Eye Field	SEF
Temporoparietal Junction	TPJ
Transcranial Magnetic Stimulation	TMS
Ventro-Lateral thalamic nucleus	VL
Ventral Frontal Cortex	VCF
Voluntary Saccade	VS

NB: Acronyms are always first defined in the text before being used as abbreviations.

State of the art



1. Exploring the word with the eyes

1.1. Visual perception

Long time has passed since the ancient Greeks who believed that the eye was throwing visual fire on objects to sense their form, colors and other properties. In the tenth century, the Persian Ibn Al Haytham speculated that the eye actually receives light sent by the object and some six centuries later, Johannes Kepler gave back to Cesar (the retina) its role in the visual sense. Finally, Descartes (*Traité de l'homme*, 1633) first postulated a relationship between light signal received by the eyes and the brain. The following section will try to expose the actual understanding of visual perception, namely the process that interprets the surrounding environment using the visible light spectrum (from 380 to 780 nm).

1.1.1. Before all, there was the eye

1.1.1.1. The organ

When you close the eyes, you cannot see, people with no eye cannot see. Therefore, the eye seems to be necessary for vision (Figure 1). These eyes allow humans to have a binocular visual field of 135° vertical and 200° horizontal. For each individual eye, it is typically 30° superior, 45° nasal, 70° inferior, and 100° temporal.

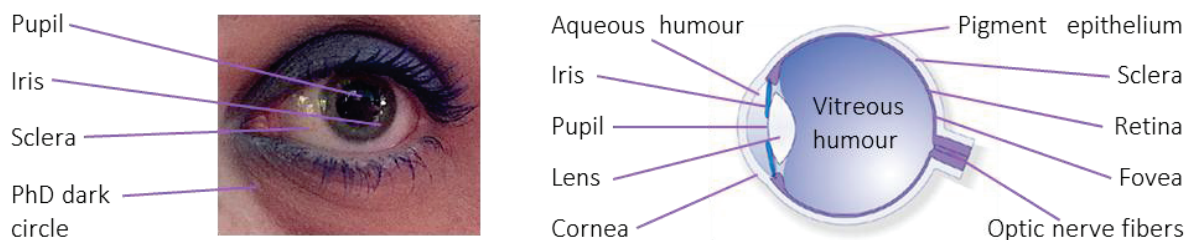


Figure 1: *The Eye. Left panel: front view of the eye. Right panel: cross section of the eye.*

The light enters the eye through the cornea which is a transparent window. It is curved and acts as a lens, namely it focuses light beam by means of refraction. The eye part named lens acts also as a lens. Yet, even though this part is eponymous, it is actually the cornea which has the biggest focusing power. The lens' purpose is to focus light onto the retina. As the light enters the eye, it is bended, the proportion of bending actually depends on the lens that can be either thickened or tightened. People with lens bending issues wear glasses. The amount of light entering the eyes is set by the aperture in front of the lens, the pupil. The iris, the colored part of our eyes, constricts when light level is too high and the pupil thus becomes smaller. The pupil might also shrink to get a better depth of focus, just like cameras. The eye is filled with the vitreous humour that keeps the eye in shape and pins the retina at the back of the eye. The retina is the light-sensitive layer of the eye, the one doing the actual job of transforming the

physical signal composed of photons into a brain readable electrochemical signal (action potentials). This layer is composed of photoreceptors, horizontal cells, and Amacrine cells (also horizontally organized). The horizontal and amacrine cells are locally connected and perform inhibitory regulations to the photoreceptors or the retinal ganglion cells which we will both present further below.

1.1.1.2. The photoreceptors of the retina

The photoreceptors lie at the back part of the retina, *i.e.* there are a lot of things between them and the incoming light (Figure 2). There are nine important points to know about them (almost managing up to Moses' 10 important points). (1) They come with two modulations: cones or rods (named from their shape). (2) Rods all contain rhodopsin photopigments which are sensitive to green light and reflect red and blue light (more or less purple). (3) Cones are responsible for color vision since they come in three main light-sensitive types. 'Red' cones are sensitive to long wavelengths light, green cones to middle wavelengths, and 'blue' cones to short wavelengths. (4) Rods are responsible for dim light vision (scotopic vision) while cones are more active in full light conditions (photopic vision). When both are active, it is mesopic vision. (5) The overall cone system is more sensitive to yellow light. (6) The repartition of cones and rods on the retina is not even. The fovea is highly cone concentrated while peripheral vision relies more on rods. (7) There are no blue cones at the very center of the fovea. (8) Both photoreceptor types are absolutely absent in a region about 12-15° of eccentricity into the nasal retina because blood vessels and ganglion cell axons leave the eye at that point called the blind spot. Fortunately, we have two eyes and each blindspot points towards an opposite direction that is the reason why we do not experience a hole in our visual field. And... (9) Colorblind people miss one cone type (sometimes two).

1.1.1.3. The retinal ganglion cells



Figure 2: Retinal cells. Left panel: Schematic representation of the different cells composing the retina. Middle panel: scanning electron micrograph of a primate retina. Right panel: density of rods and cones as a function of eccentricity (adapted from Snowden et al., 2011).

The retina is also composed of retinal ganglion cells (Figure 2). The photoreceptors send their message to these retinal ganglion cells *via* the bipolar cells. The axons of the ganglion cells leave the eye through the blind spot and travel up to the Lateral Geniculate Nucleus (LGN) which we will come back to later. These cells have an interesting property: the Receptive Field (RF) (Lennie, 2003). This RF is important to

define since this property is shared by many neuronal population. The RF is the particular region of the sensory space in which a stimulus will modify the firing of that neuron. In the present case, the RF of the retinal ganglion cell is the area on the retina over which light will influence the firing rate of this particular cell. This RF is composed of a region for which light increases the baseline activity (ON region) and a region for which light decreases the baseline activity (OFF region) (Figure 4). They come in two types: ON-center cells with maximum excitation when light hits the center and OFF-center cells with maximum inhibition when light hits the center. These receptive fields need a change of luminance occurring to change their baseline activity, this could be represented by an edge for example. The ganglion cells are integrating information and not only responding to raw physical stimuli. We thus can say that they are the first step of visual perception.

1.1.1.4. On the way to the brain: the optic nerve

Vesalius was the first, in *De Humani corporis fabrica* (1543), to describe the macroscopic anatomy of the brain, including the optic nerve and the optic chiasm (Figure 3, lower right).

The optic nerve is composed of the axons of the ganglion cells. Each optic nerve (extending from each eye) travels up to the optic chiasm situated below the hypothalamus, which is situated at the bottom of the brain. At the optic chiasm the ganglion cell axons perform a partial decussation: axons extending from the nasal retina cross and axons from the temporal retina do not cross. Therefore, after the optic chiasm information is segregated into the right and the left visual fields: the right optic tract carries information about the left visual field and the left optic tract carries information about the right visual field (Figure 3, left). These optic tracts project mainly to the LGN. Ten to twenty percents project to other structures such as the superior colliculus (SC).

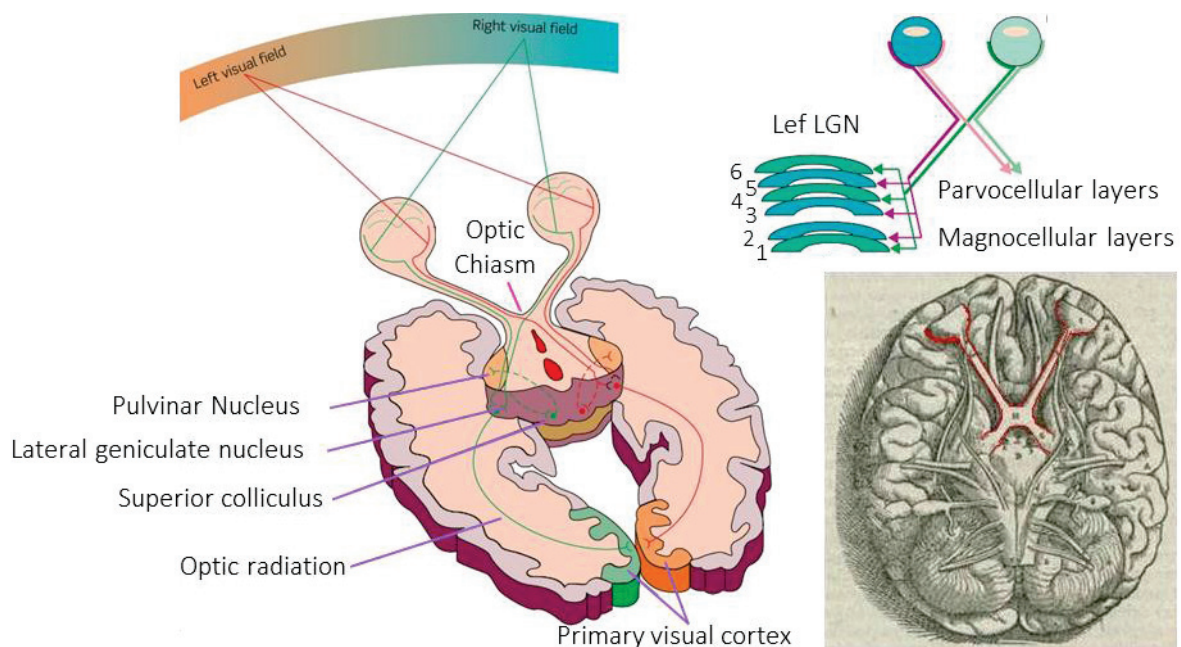


Figure 3: Visual pathway to the cerebral cortex. **Left panel:** Schematic representation of the optic pathways (adapted from Snowden et al., 2011). **Upper right panel:** Projection of optic information on the different layers of the Lateral Geniculate Nucleus (LGN). **Lower right panel:** The optic chiasm in *De Humani corporis fabrica* of Andreas Vesalius.

1.1.2. The eye senses but the brain sees

'Point d'yeux sans cerveau, point de cerveau sans yeux' (Diderot) which can be translated as “no eye without brain, no brain without eye”. While this quote seems a little be exaggerated especially when you consider people with no eyes, it still raises the important point that visual perception is a whole that requires the eye to be functioning as well as a brain to interpret information flowing from the eyes.

1.1.2.1. From the retina to the brain through the lateral geniculate nucleus

The LGN is a rather complicated structure for which we will not go into much details. Although it is important to know that it is composed of 6 layers (Figure 3, upper right). Four of them are called the parvocellular layers and two of them, the magnocellular layers. The ganglion cells are also of two types, the parvocellular (P cells) and magnocellular types (M cells). The M cells reach the magnocellular layers and the P cells reach the parvocellular layers. Half of these layers receive inputs from the left eye, and the other half from the right eye. In the LGN, cells are organized in a retinotopic mapping which means that the spatial organization of the ganglion cells is preserved in the LGN. The magnocellular and the parvocellular pathways have different properties. The former is more specialized in movement detection while the latter is more specialized in color vision. Between the six layers of each LGN lie the koniocellular cells which receive input from very special ganglion cells that have a pretty privileged relationship with blue cones. The properties of the LGN look like the ganglion cell properties. However, the major input (approximately 80%) to the LGN does not come from the retinal ganglion cells but from the cortex, *i.e.* top-down. This raises the interesting idea that already at the LGN level, top-down factors filter the information going to the cortex... But this story is not yet to be told.

1.1.2.2. Low-level visual areas: the striate cortex

The optic radiations then leave the LGN to reach the occipital cortex, the part of the brain that is further away from the eyes, at the back of the head. Here, at the extreme tip of the occipital lobe, there is the primary visual cortex (V1). As the rest of the neocortex, V1 is composed of 6 cell layers. At this level of the visual processing, inputs from the left and right eyes are still segregated. The Layer 3 receives inputs from the koniocellular cells, the parvocellular layers of the LGN send inputs to the layer 4A and 4C β . The magnocellular layer sends inputs to the layer 4C α . The organization is still retinotopic. Yet, the retinotopy at the level of V1 is distorted, much more cortical surface is dedicated to the fovea and the central visual field as compared to the rest of the visual field. The more peripheral, the less cortical surface.

Strikingly, contrary to the retinal ganglion cells, V1 cells are not light sensitive, but rather are orientation-selective (Hubel and Wiesel, 1959). Each cell responds maximally for a preferred orientation, this response decreases when you move away from the preferred orientation. The distribution of the number of spikes around the preferred orientation is called a ‘tuning curve’. Actually, the cells responsible for this strict orientation selectivity are the simple cells, they are phase sensitive. Their RF also possess ON and OFF regions except that the organization is not circular and the two elongated zones representing OFF-regions enclose the elongated zone representing the ON-region (Figure 4). When the stimulus perfectly lies in the ON-region, response is maximal. Simple cells send this integrated information to complex cells. Complex cells have also preferred orientation, but contrary to simple cells, their responses are not discrete and since they receive inputs from several simple cells (preferring the same orientation), they fire whenever one of these simple cells fires. When more simple cells fire, the

complex cell fires more reaching its maximum when the length of the bar matches the length of the complex cell receptive field. And now, the hypercomplex cells. These cells are actually not hyper complicated, instead of increasing their firing rate when the bar becomes bigger in the RF just like the complex cells, they have a preferred length for which they fire the most (Snowden et al., 2011).

To sum up, in V1, there are cells that are triggered by particular feature (called Trigger feature cells), for example some cells will fire for a 15°-tilted-5-cm-moving-to-the-right bar. V1 is therefore involved in many vision features such as motion direction, color, and binocular disparity.

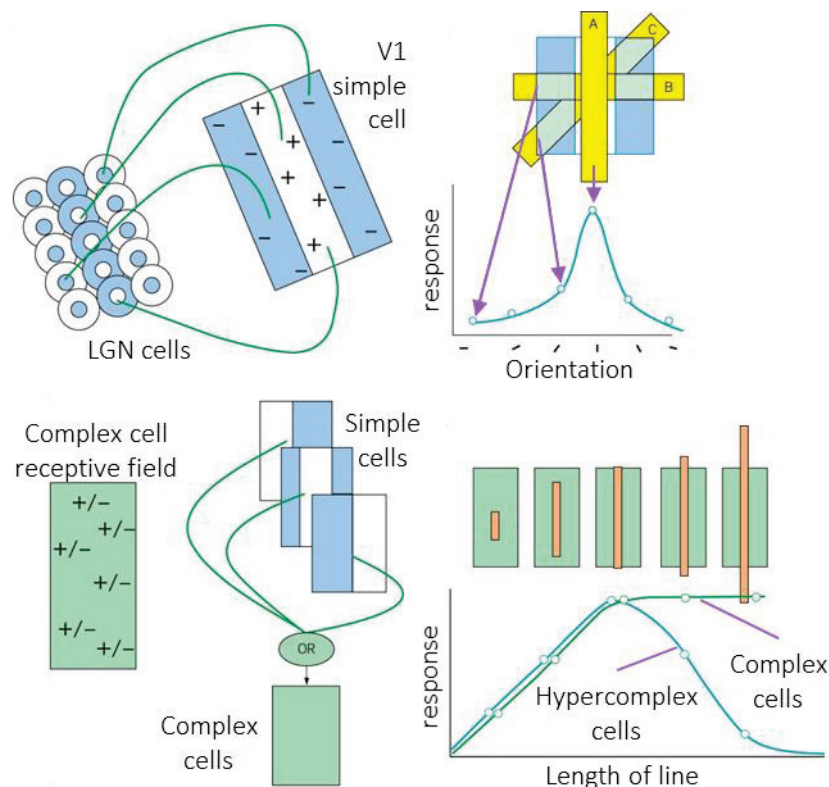


Figure 4: Trigger feature cells of the primary visual cortex (V1). Upper panels: Schematic representation of the Lateral Geniculate Nucleus (LGN) inputs to V1 simple cells (left) and orientation tuning curve (right). Lower panels: Schematic representation of the simple cell inputs to V1 complex cells (left) and tuning curve of complex and hypercomplex cells (right) (adapted from Snowden et al., 2011).

1.1.2.3. Higher-level visual area: extrastriate cortex

Talking about the extrastriate cortex is a little bit ambitious since it concerns all the areas outside V1 that are involved in visual processing, which corresponds to more or less 30 areas. These areas are found in the occipital lobe (V2, V3, V4, V5 etc.), in the parietal lobe, and in the temporal lobe. In the early times, each area was thought to be specialized in one kind of processing only, for example, V5 would be specialized in motion detection and nothing else. And indeed, the impairment of this area leads to this disabling condition, called akinetopsia, in which patients see life as in a club using stroboscope.

State of the art

However, time flies and concepts change. The complexity of the extrastriate cortex is partly due to the forward and backward connections between all the areas (Figure 5, upper panel). These two-direction connections prime the idea of two main components in vision. The first one is the bottom-up processing that emerges from the stimulus itself, *i.e.* the transduction from the light energy into neural signals in the dedicated areas, namely the striate cortex. The second one is the top-down processing. In this case, the brain actually uses contextual cues and former knowledge to provide expectations which help understand what we experience in the environment, this process is underpinned by the associative areas.

Besides this first dichotomy, in an influential paper of Goodale and Milner (1992), vision has also been divided into two streams: vision for perception in a ventral stream (the 'what' stream) and vision for action in a dorsal stream (the 'where' stream, that could also be called the 'how' stream) (Figure 5, lower panel). In this simplified useful framework, the 'what' stream travels down to the inferotemporal cortex through V4 and processes information in an object-centered manner to identify and discriminate objects (shape, size, etc.) while the 'where' stream is passing by V5 to reach the PPC and processes information in an egocentric manner to provide information on how to act on objects (body position in relation to object location). In this latter case of vision-for-action, the outcomes are visuomotor behaviors.

These goal-directed movements require hence to know exactly where in space objects are located to accurately target them. The visuomotor integration allows to transform these visual signals in egocentric coordinates to plan a motor commands sent to muscle effectors. These effectors can be the arms, the legs, but also, and even more significantly, the eyes.

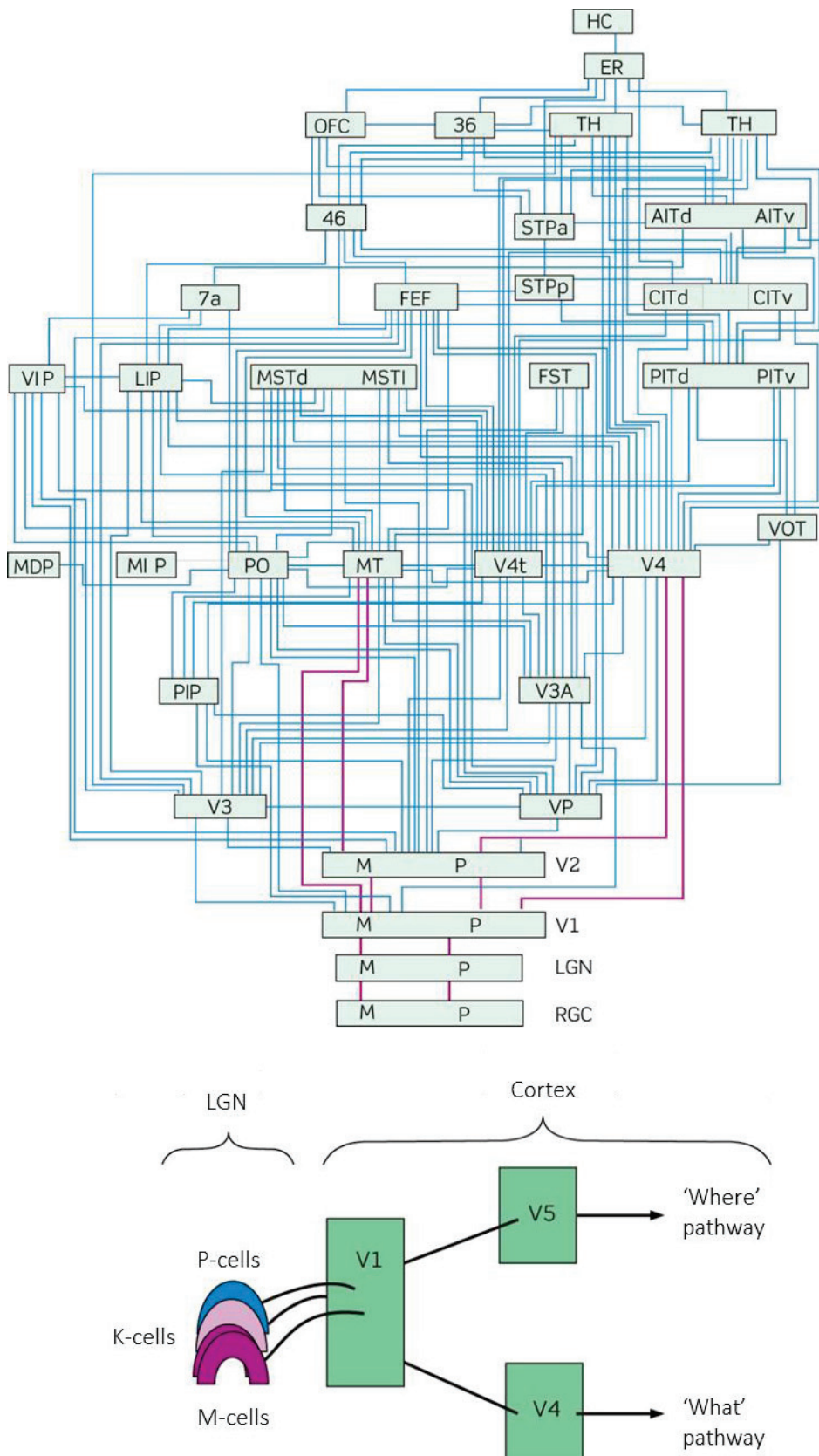


Figure 5: Organization of cerebral visual areas. Upper panel: complicated scheme of the known connections between brain areas processing visual information (adapted from Felleman and Van Essen, 1991). Lower panel: safe simplification of the visual pathways (Snowden et al., 2011).

1.2. Saccadic system

Eye movements are of outmost importance since they aim at bringing and stabilizing objects of interest on the fovea, allowing a better visual perception of these objects. Eye movements are at the crossroads of vision for action and vision for perception. Their study, as well as their link with perception, has then great implications for our understanding of the human behavior. Indeed, eye movements are great revelators of our goals and cognitive strategy and '*Eyes are the windows of the soul*' might be more than a cheesy quote.

1.2.1. Different types of eye movements and their role

There are four basic types of eye movements. Smooth pursuit eye movements allow to track a moving target. The vestibulo-ocular and optokinetic reflexes stabilize the eyes relative to the relative motion between our head and the external world. The vergence movements align our two foveae onto objects at different distances from our head. And, finally, saccades are ballistic eye movements that rapidly bring the fovea onto an object of interest in the visual field (Leigh and Zee, 1999). Saccades are the fastest movements the body can make, which allows human to make around 3 saccades per second. **This PhD work will focus on this latter type, namely saccadic eye movements.**

1.2.2. Saccade characteristics

Saccades are the rapid eye movements that move our eyes from one visual target to another. During saccades, the eyes rotate as fast as 500 deg.s^{-1} and these movements are usually less than 50 ms. This brevity is optimized to view larger number of targets while minimizing the saccadic transit time during which vision is impaired. Saccadic eye movements can be described by their latency and by three main kinematic variables linked together by the main sequence relationships: the amplitude (or gain), the duration, and peak velocity.

1.2.2.1. Amplitude and gain

Amplitude is the difference between the position before and after the saccades. Most of the time, the saccadic gain is used to measure the accuracy of saccades irrespective of the target eccentricity. The gain is the ratio between the actual amplitude of the saccade and the desired amplitude of the movement to perfectly land on the target. In this case, the gain is 1 and the saccade is said normometric. When the eyes overshoot the target (gain > 1), the saccade is said hypermetric, when the eyes fall short (gain < 1) the saccade is said hypometric. Actually, normal subjects show a tendency to undershoot (gain between 0.9 and 0.95 depending on the saccade type). The reason of this undershooting is still a matter of debate. It has first been suggested that the hypometria of saccades is meant to maintain the neural representation of the target in the same hemisphere as before the saccade (Robinson, 1975) and thence allowing faster processing. It has also been suggested that it is an economical strategy to minimize overall saccade flight time (Harris, 1995). Primary hypometric saccades are usually followed by a corrective saccade.

1.2.2.2. Latency

The latency of saccades has received extensive interest in the literature since it reflects several cognitive processes such as visual processing and attention, target selection, decision making, and motor planning. The saccade latency depends on different factors such as stimulus content, type of saccade or task at hand, varying between 150 ms and 500 ms.

1.2.2.3. Main sequence: duration and peak of velocity

Saccades have this particularity of having a consistent relationship between amplitude and peak velocity (highest velocity reached during the saccade), as well as between amplitude and duration (Bahill et al., 1975). These relationships are called together the main sequence. The relationship between the duration and the amplitude is linear up to 50° amplitudes whereas the link between the peak velocity and the amplitude rises steeply for amplitudes less than 25° and then saturates (Leigh and Zee, 1999).

1.2.3. Triggering saccades

Saccades are mainly categorized as either (1) **Reactive Saccade** (RS) that is triggered by a sudden change in the visual field, or (2) **Voluntary Saccade** (VS) that is intentionally driven to explore a stable environment (Gaymard et al., 1998a).

Typically, RS are elicited within 200 ms. In the laboratory, RS are elicited with the target step paradigm. The fixated stimulus jumps suddenly to another location and subjects are instructed to follow the stimulus as fast and as accurately as possible.

VS have longer latency than RS, typically 250 ms. Also, because of their endogenous triggering, there are several paradigms to elicit them. For the classical VS consisting of scanning saccades, stimuli are simultaneously displayed and subjects are instructed to explore the visual scene at their own pace. The memory-guided saccades necessitate to remember the position of a previously presented target which is no longer visible at the time of the saccade initiation. The predictive saccades are made for example when looking at two targets which regularly alternate. Finally, Anti-Saccades (AS) are elicited when subjects are instructed to look at the mirror location of a visual stimulus.

1.2.4. Corollary discharge, aka Efference copy

Efficient motor control, especially of ballistic eye movements such as saccades, faces two major issues. First, the sensory feedback is noisy and delayed; for saccades, visual feedback is actually available only after the completion of the movement due to the saccadic suppression phenomenon which involves that visual sensitivity is drastically reduced during saccade execution (Bridgeman et al., 1975). Second, the relationship between a motor command and the movement is variable as the body position changes. Therefore, the computational solution that arises is to build adaptive internal models of the environment and of our moving body. It comes to predict the consequences of our movement on our environment, namely the sensory feedback that will be received by the brain at the end of the movement (Shadmehr et al., 2010). Predicting sensory consequences is achieved by forward models

and in the case of saccades, the terms that were first brought up was either efference copy by von Holst and Mittelstaedt (1950) – if you wonder whether I can read German, my only answer will be that there is an English version - or corollary discharge (CD) by Sperry (1950). As Sommer and Wurtz (2002) argued, we will prefer the term corollary discharge in this manuscript because of the more generalized concept and the fact that this signal is not a literal copy of the motor command *per se*, *i.e.* the one that is sent from the motoneurons to the muscles (Bridgeman, 1995).

Tickling can help here to understand the concept of the corollary discharge. When you tickle yourself (which you certainly do every day), you are not sensitive to these tickles. However, when someone else does, it is an entirely other story. Actually, in the former case, we are not sensitive when we are tickling ourselves because our brain has predicted the consequences of our own movements on our mechanoreceptors. The CD is the signal conveying the prediction of these consequences. It has been first thought as a mechanism that allows the brain to make the difference between exafference, *i.e.* motion perceived by the retina due to change in the environment and reafference, *i.e.* motion perceived by the retina induced by our own movements. In the case of eye movements the CD has been proved to contribute to visual stability across saccades in both humans (Ostendorf et al., 2010) and monkeys (Cavanaugh et al., 2016a) by encoding the size and the direction of the upcoming saccade and allowing the visual areas to predict retinal displacement and compensate for it. Sommer and Wurtz (2004) identified a pathway from the SC through the thalamus to the Frontal Eye Field (FEF) which might transport the CD signal. Cavanaugh et al. (2016a) reported results on patients with cerebellar lesions which suggested that part of the CD processing is subtended by the cerebellum.

The CD is also valuable in planning sequential saccades in a delayed double step paradigm for example. In this task, two targets are flashed sequentially and one has to remember their locations before starting the saccade sequence. The CD allows to take into account the consequences of the first saccade to plan the second saccade even before landing at the first target position. The planning of two saccades in parallel has actually been proved to be possible and therefore, the CD becomes even more important in this situation (Walker and McSorley, 2006).

Finally the CD is also used in the motor adaptation. Once the saccade has begun, retinal input cannot modify this movement in-flight, therefore, the error feedback available after saccade termination is useful only in the planning of subsequent saccades. This is called an open-loop feedforward system (Bridgeman, 1995).

1.2.5. Oculomotor plant

1.2.5.1. Three dimensional rotations

The eyes rotate around three axes, the parasagittal X-axis, the transverse Y-axis, and the vertical Z-axis. The intercept of these three axes passes through the center of the eyeball. The six Extraocular Muscles (EOM) have different actions on the eye (Table 1).

Table 1: Actions of the Extraocular muscles

MUSCLE	PRIMARY ACTION	SECONDARY ACTION	TERTIARY ACTION
Medial rectus	Adduction	-	-
Lateral rectus	Abduction	-	-
Superior rectus	Elevation	Intorsion	Adduction
Inferior rectus	Depression	Extorsion	Adduction
Superior oblique	Intorsion	Depression	Abduction
Inferior oblique	Extorsion	Elevation	Abduction

1.2.5.2. Extraocular muscles

The eyeball is suspended in the cone shaped orbit. Each eye is rotated by three pairs of antagonistic EOM, the lateral and medial rectus muscles, the superior and inferior rectus muscles, and the superior and inferior oblique muscles. As often, in anatomy, one picture is worth a thousand words: Figure 6.

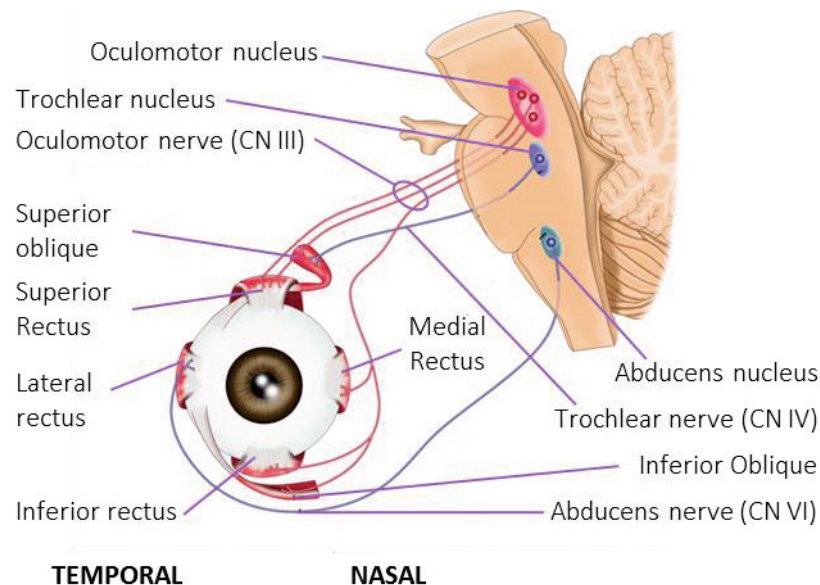


Figure 6: Organization of the cranial nerve nuclei and the extraocular muscles they innervate. Only the the right eye is represented.

Binocular vision is ensured by conjugate eye movements which in turn result from the synergic action of the EOM. Each EOM is associated to an antagonist but also an agonist/antagonist EOM couple involved in the movement of the other eye. For example, the lateral rectus of the left eye is agonistic to the medial rectus of the right eye but antagonistic to the medial rectus of the left eye and the lateral rectus of the right eye. These relationships obey two laws: (1) Hering's law which stipulates that during

a binocular conjugate movement, the agonistic muscles of the two eyes simultaneously receive equal nervous inputs; (2) Sherrington's law which stipulates that activation of a muscle is associated with inhibition of its antagonistic muscle. **This PhD work will focus on horizontal saccadic eye movements involving mainly the lateral and the medial rectus muscles.**

1.2.5.3. Innervation of the extraocular muscles

The EOM are innervated by motoneurons which axons form the cranial nerves III, IV, and VI (Figure 6). The abducens nerve (VI) exits the brainstem from the ponto-medullary junction and innervates the lateral rectus muscle. The trochlear nerve (IV) exits from the caudal portion of the midbrain and supplies the superior oblique muscle. Contrary to all other cranial nerves, the trochlear nerve exits from the dorsal surface of the brainstem and crosses the midline to innervate the superior oblique muscle on the contralateral side. The oculomotor nerve (III), which exits from the rostral midbrain near the cerebral peduncle, supplies the remaining four EOM.

1.2.6. Neural substrates of saccade production: from the central nervous system to the periphery

Since saccades are ballistic, stereotyped movements, their neural substrates, at least at the motor level have been extensively investigated and are now well understood.

1.2.6.1. Cortical substrates

Performing a saccade requires a visuomotor transformation, namely the system needs to translate the spatial coordinates of the selected target encoded retinotopically in visual areas, into a motor vector (defined by an amplitude and a direction). This visuomotor transformation mainly relies on cortical areas such as the FEF and the Parietal Eye Field (PEF) (Figure 7, left).

The posterior parietal cortex

The PPC integrates information about the body position relative to any movement goals. It has been postulated that the motor goal of a saccade is encoded in the PPC and is reflected as an increase of Gamma Band oscillatory Activity (GBA) (above 35 Hz) (Van Der Werf et al., 2008). It then sends this information to different cortical areas before reaching the SC. The next cortical area depends on the type of saccade about to be produced. For RS, a subset of the PPC is involved and has been called the PEF. The PEF is situated in the posterior IntraParietal Sulcus (IPS). Its involvement in RS has been suggested by reports of longer latency of RS, but not VS, after its lesion (Pierrot-Deseilligny et al., 1987) Pierrot-Deseilligny et al., 1991; Lynch and McLaren, 1989; Pierrot-Deseilligny et al., 2003). Also, after lesion of the PEF, contraversive RS gain decreased (Gaymard et al., 1998b). RS are elicited thanks to direct connections between the PEF and the SC (Lynch et al., 1985). The PEF is also connected to oculomotor frontal areas. These connections are reciprocal.

Oculomotor frontal areas

In the frontal cortex, several areas are involved in the control of saccades. First, the main one is the FEF. This area is situated at the junction of the prefrontal sulcus and the superior frontal sulcus. Lesions of this area are associated with longer latency of VS (visually-guided and antisaccades) and with inaccuracy of memory-guided contralateral saccades (Gaymard et al., 1998a). Neurophysiological data confirmed the involvement of the FEF in VS. Indeed, Bruce and Goldberg (1985) found that the activity of pre-saccadic movement neurons was maximal before VS and absent before RS. The FEF is connected to the saccadic Brainstem Burst Generator (BBG) *via* three main pathways: (1) a direct pathway towards the pons; (2) an indirect pathway through the SC; and (3) an indirect pathway passing by the Basal Ganglia (BG) (caudate nucleus and substantia nigra) and the SC.

Second, the dorsolateral Prefrontal Cortex (PFC) is involved in the memory component of saccades and in inhibition. Indeed, RS are not affected by lesions of the dorsolateral PFC (Pierrot-Deseilligny et al., 1991). However, if the instructions change, *i.e.* if subjects are instructed to saccade towards the mirror position of the visual target, an increase of directional errors (*i.e.* saccades towards the actual stimulus) is observed as compared to control subjects, providing evidence that the dorsolateral PFC is involved in the inhibition of the RS (towards the visual target). After lesion of this area, patients are also impaired with memory-guided saccade becoming inaccurate. Patients' observations are consistent with monkey lesion studies (Funahashi et al., 1993; Funahashi et al., 1989).

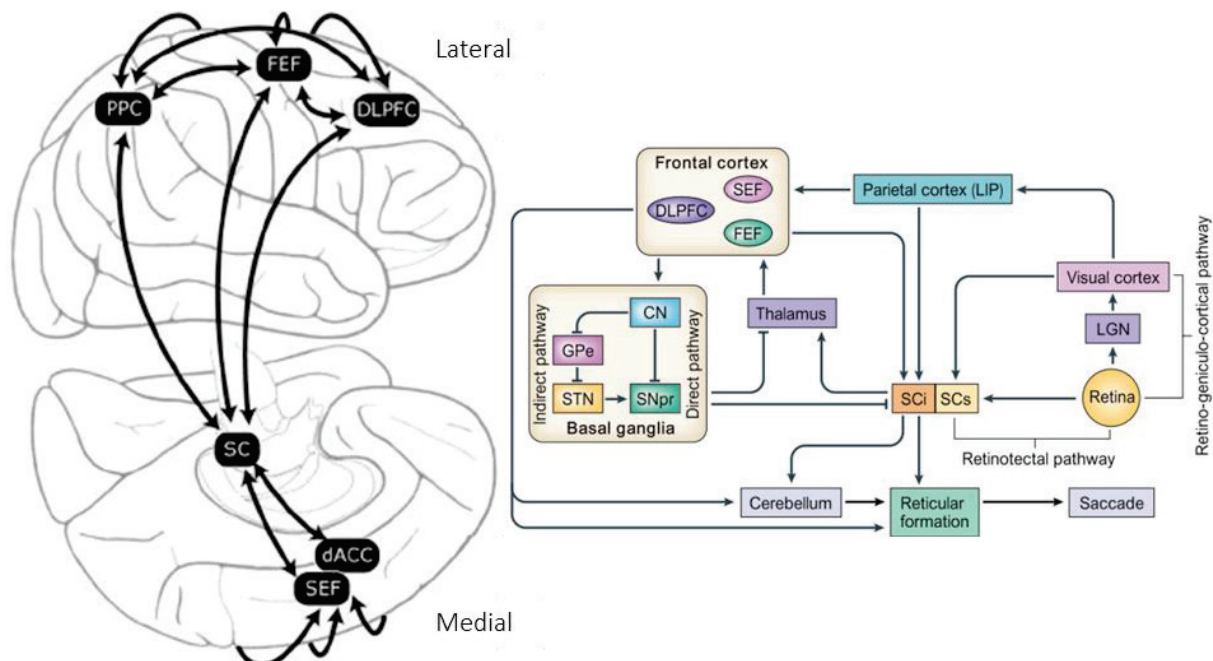


Figure 7: Cortical and subcortical networks involved in saccadic eye movements. **Left panel:** Key connections between nodes of the oculomotor network in the human cerebral cortex. SC = Superior Colliculus; PPC = Posterior Parietal Cortex; FEF = Frontal Eye Field; DLPFC = Dorsal Lateral Prefrontal Cortex; SEF = Supplementary Eye Field; dACC = dorsal Anterior Cingulate Cortex (adapted from Curtis and D'Esposito, 2009). **Right Panel:** Saccade production circuitry. LGN = Lateral Geniculate Nucleus; LIP = Lateral IntraParietal (monkey equivalent of the human PEF); SCi = Superior Colliculus intermediate layers; SCs = Superior Colliculus superficial layers; GPe = external segment of the Globus Pallidus; STN = Subthalamic Nucleus; CN = Caudate Nucleus; SNpr = Substantia Nigra pars reticulata (adapted from Munoz and Everling, 2004).

Third, the frontal cortex hosts the Supplementary Eye Field (SEF) in the region of the paracentral sulcus. This area is not involved in the production of saccades *per se* but lesion of the SEF is reflected by impairments in memory-guided sequences of saccades (Gaymard et al., 1990). Moreover, a fMRI study confirmed this observation in healthy subjects (Heide et al., 2001).

Finally, in the anterior cingulate cortex, an area has been postulated to be part of the cortical oculomotor network. Indeed, lesions of this cingulate eye field yield deficit in VS (Gaymard et al., 1998b).

1.2.6.2. Subcortical areas

The basal ganglia

The basal ganglia found right in the middle of the brain, are a relay for oculomotor information between the FEF and the SC (Hikosaka et al., 2000). In the bunch of nuclei of the BG, two are of particular importance for saccades: the Caudate Nucleus (CN) and the substantia nigra pars reticulata. The FEF projects to the CN which in turn sends inhibitory projections onto the substantia nigra pars reticulata. Finally, the substantia nigra pars reticulata inhibits the SC in a tonic fashion and therefore prevents saccade production. BG are therefore involved in the VS initiation and in maintaining fixation.

The superior colliculus

The superior Colliculi lie below the thalami at the roof of the mesencephalon. As we have seen above, all the cortical areas involved in saccadic eye movements project to the SC. The SC is indeed, the major relay between afferent cerebral inputs and efferent subcortical inputs and therefore plays a central role in visuomotor integration. It is the first common structure involved in all types of saccades.

The SC is composed of three superficial layers and four deep layers. The superficial layers of the SC contain visual retinotopic maps with the rostral pole responding to stimuli near the fovea and the caudal pole responding for more peripheral visual stimuli (Goldberg and Wurtz, 1972). They receive inputs from the retina and the visual cortex. These visual layers project to the deep sensorimotor layers of the SC.

The deep layers of the SC are involved in the orientation of the gaze with or without eye movements (gaze orientation results from combined movements of the eye, head, and eventually body) (Wurtz and Albano, 1980). Some cells in the SC are Saccade-Related Burst Neurons (SRBN) and connect to the BBG. They start to discharge a compact burst about 20 ms before the actual onset of preferred saccades (Sparks and Jay, 1986). These neurons have motor fields, namely they discharge for a preferred motor vector defined by a direction and an amplitude (Figure 8). The rostro-caudal axis relates to the amplitude of the saccade while the lateral-medial axis relates to the verticality of a saccade (Mohler and Wurtz, 1976; Sparks et al., 1976). Therefore, while the direction and the amplitude of the saccade are encoded by the location of the active SRBN population on the motor map (Wurtz and Goldberg, 1972), the velocity and duration of the saccade are determined by the temporal characteristics of the SRBN burst. Interestingly, despite this central role of the SC in the oculomotor system, a lesion of the SC does not abolish saccade production, suggesting parallel pathways allowing to compensate after such lesion.

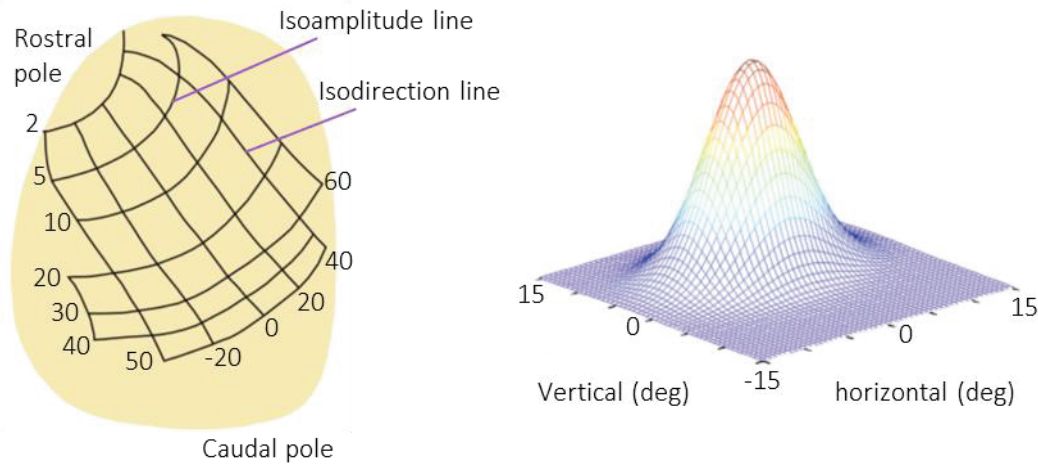


Figure 8: Saccadic motor map of the Superior Colliculus (SC). *Left Panel:* The map of eye movements in the primate SC revealed by applying electrical stimulation. The amplitude and direction of saccadic eye movements are determined by the site of stimulation in the SC. *Right Panel:* Schematic representation of the movement field of a saccade-related neuron in the deeper layers of the SC. The neuron activity level is indicated by colour contour plot (adapted from King, 2004).

From the deep layers, there are three main pathways. The first one sends descending inputs to the BBG, the second one sends descending inputs to the Oculomotor Vermis of the cerebellum (OMV) *via* the nucleus reticularis tegmenti pontis (NRTP) (Scudder et al., 1996; Thielert and Thier, 1993) and the last one sends ascending inputs to the cerebral cortex *via* thalamic relays. Concerning such SC-thalamo-cortical relationships, one pathway in particular allows the SC to transfer a “copy” of the movement to the FEF *via* the Medial Dorsal thalamic nucleus (MD). As already detailed above, this corollary discharge allows the system to predict the sensory consequences of the upcoming movements (Sommer and Wurtz, 2002; Sommer and Wurtz, 2008).

Aside the SRBN, the SC contains, at its rostral pole, fixation neurons. They are active during fixation and cease firing shortly before saccade initiation, thus contributing to prevent unwanted saccades towards distractors (Munoz and Wurtz, 1992; Munoz and Wurtz, 1993a; Munoz and Wurtz, 1993b). These neurons project to BBG omnipause neurons (OPN) (Paré and Guitton, 1994).

1.2.6.3. The saccadic burst generator of the brainstem

The saccadic brainstem burst generator lies in the reticular formation (Figure 10, left). It receives signals from the deeper layers of the SC. The BBG neurons responsible for **horizontal saccades, which this PhD work is about**, lie in the ipsilateral paramedian pontine reticular formation, the contralateral medullary reticular formation, the bilateral nuclei prepositus hypoglossi, and medial vestibular nuclei (King and Fuchs, 1979). The activity of the BBG is then transmitted to motoneurons of the oculomotor nuclei which, in turn, activate agonistic muscles and inhibit antagonistic muscles.

For a horizontal saccade, the BBG sends command to the abducens nucleus from which the abducens nerve (cranial nerve VI) emerges. The BBG is the source of the pulse-step innervation of the motoneuron signals (Figure 9) (Robinson, 1970). Before a lateral saccade, the abducens motoneurons generate a vigorous burst of spikes (pulse signal) which duration is approximately equal to the duration of the saccade (Scudder et al., 2002). This pulse corresponds to the phasic signal that allows to overcome the

viscous drag of the orbital tissue and to move the eye at high speed. The pulse gradually decreases to a final step of innervation. This step is a position-related change in tonic activity and is proportional to the fixation position, namely the tonic activity increases when the distance between the new fixation position and the position for which the concerned muscle is not recruited increases. The step of innervation maintains the eye in the eccentric position fighting against elastic restoring forces that drive the eye back to its central position in the orbit. During movement in the antagonistic direction, the discharge rate of the motoneurons ceases.

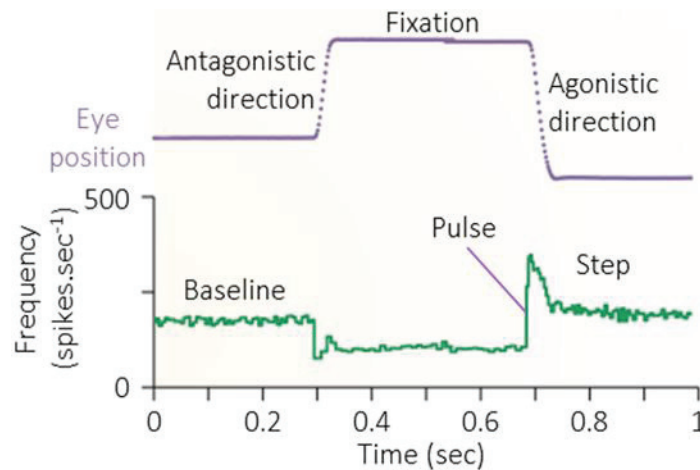


Figure 9: Discharge pattern of a motoneuron of the left abducens nucleus. The eye performs first a rightward (antagonistic direction) then a leftward (agonistic direction) saccade (purple line). The instantaneous spike frequency drops for the antagonistic direction. When a saccade is performed in the agonistic direction, the motoneuron emits a burst of spikes and then the frequency decreases to a level proportional to the eccentricity of the new eye position (adapted from Sparks, 2002).

The pulse activity is underpinned by three different types of neurons: (1) the Short-Lead Burst Neurons (SLBN) subdivided into two types: the Excitatory Burst Neurons (EBN), and the Inhibitory Burst Neurons (IBN); (2) the Long-Lead Burst Neurons (LLBN); (3) and the OPN (Figure 10, right).

The SLBN and the OPN have antagonist roles: while the SLBN emit a burst from 10 ms before the beginning of the saccade to right before its end and are silent during steady gaze, OPN discharge at a constant rate and need to be inhibited for the saccade to be initiated. SLBN are direction-specific, OPN are not; they pause regardless of the direction of the upcoming saccade. The two types of SLBN have also differentiated actions. EBN make monosynaptic excitatory connections with ipsilateral motoneurons that produce ipsiversive saccades and IBN make monosynaptic inhibitory connections with contralateral motoneurons to produce a pause in their discharge during contraversive saccades. OPN project to all burst neurons and provide monosynaptic tonic inhibition. Their pause allows the SLBN to fire and therefore is concomitant to the burst of SLBN. The pause in the OPN tonic discharge is triggered by a brief signal and then is maintained by the 'latch'. The inhibition of the OPN has also been suggested to be carried out directly by the projection from the fixation cells at the rostral pole of the SC (see for review Scudder et al., 2002).

The exact origin of the latch and trigger signals is still under debate. Indeed, contrary to Scudder et al.'s (2002) view presented in the Figure 10, it has been suggested that LLBN, among other functions, play a

role in both the trigger and latch signals. Indeed, LLBN start firing before SLBN and the OPN pause. The LLBN are found among the SLBN as well as in the paramedian pontine reticular formation. They receive projections from the SC and also from the fastigial oculomotor region (FOR), the relay between the OMV of the cerebellum and the BBG. This later connection is bidirectional since the BBG also projects to the OMV of the cerebellum.

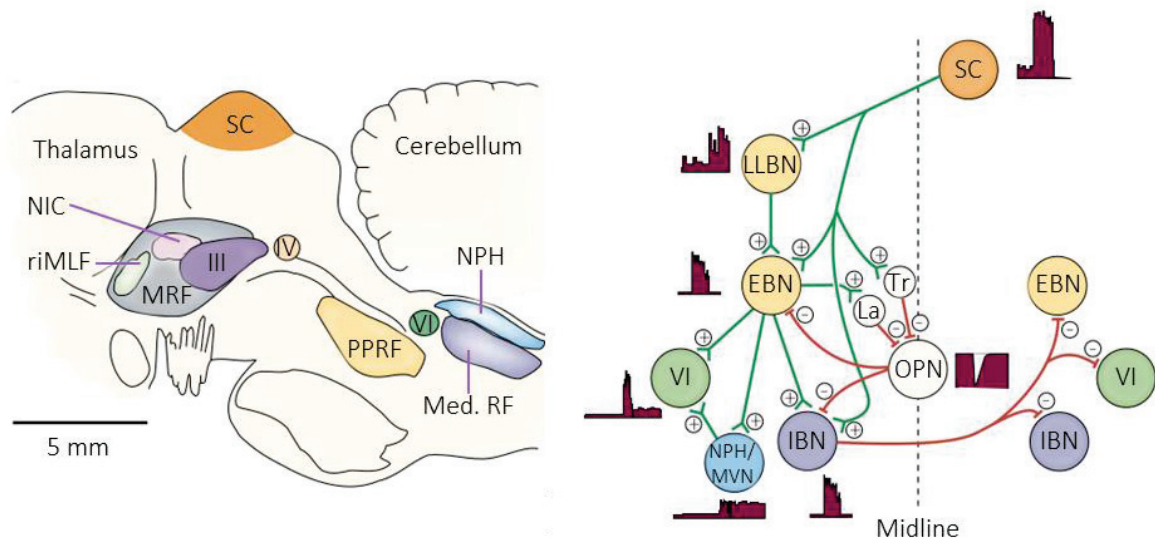


Figure 10: Locations and connections of brainstem saccade-related neurons. *Left Panel:* Monkey brainstem. III = oculomotor nucleus; IV = trochlear nucleus; VI = abducens nucleus; Med. RF = Medullary Reticular Formation; MRF = Midbrain Reticular Formation; NIC = Interstitial Nucleus of Cajal; NPH = Nucleus Prepositus Hypoglossi; PPRF = Paramedian Pontine Reticular Formation; riMLF = rostral interstitial nucleus of the Medial Longitudinal Fasciculus; SC = Superior Colliculus. **Right Panel:** Diagram of the connections of the cell types that are crucial components for horizontal saccades. EBN = Excitatory Burst Neurons; IBN = Inhibitory Burst Neurons; LLBN = Long-Lead Burst Neurons; MVN = Medial Vestibular Nucleus; OPN = Omnipause Neurons. Saccades are initiated by a trigger signal (Tr) that inhibits the OPN. The OPN are prevented from resuming their tonic discharge during the generation of the saccade command by the activity of 'latch' neurons (La) (adapted from Sparks, 2002).

1.2.6.4. The cerebellum on the sidewalk

The cerebellum is located at the bottom of the brain, underneath the occipital cortex and behind the brainstem (Figure 11, up). Contrary to the cerebral cortex, the cerebellar cortex is composed of three cell layers. Lobules VII and VIc of the cerebellum receives inputs from the SC but also from the FEF *via* the NRTP and from the BBG as aforementioned. These cerebellar regions have been named oculomotor vermis because it contains saccade-related neurons that, when microstimulated, elicit contraversive saccades (Noda and Fujikado, 1987).

The cerebellum has two main types of afferences: (1) the climbing fibers and (2) the mossy fibers. The climbing fibers project on the Purkinje cells and the FOR neurons (Figure 11, down). These axons come from the inferior olive (IO) which receives inputs from the SC. The climbing fibers are responsible for the complex-spike activity of the Purkinje cells. These complex-spikes are a fast succession of 2 to 4 action potentials (Keller, 1989). The climbing fibers are suggested to encode the error signal resulting from the comparison between the predicted sensory consequences (from the corollary discharge) and the actual sensory consequences of the motor response. This point will be developed later.

State of the art

The mossy fibers project to the lobule VII and come bilaterally from the NRTP and from dorsolateral pontine nuclei (receiving inputs from the FEF). The mossy fibers activation of the Purkinje cells leads to simple-spike activity (Keller, 1989).

Purkinje cells of the OMV project to the FOR. The FOR makes excitatory connections with the SLBN and LLBN in the contralateral BBG. This cerebellar side-loop is believed to make adjustment of the ongoing saccade trajectory through a local feedback control. FOR neurons increase their spontaneous firing rate 10 to 20 ms before the onset of a contraversive saccade. This activity might increase the ongoing discharge of contralateral IBN and EBN (Robinson and Fuchs, 2001). FOR neurons also increase their activity for ipsiversive saccades and, in this case, the burst starts when the saccade is underway. This late burst of FOR neurons is supposed to excite the EBN of the saccade antagonist muscles and/or excite IBN which in turn would inhibit agonist EBN, thus helping to terminate the ongoing saccade by contracting antagonist and relaxing agonist muscles. The FOR is thus involved in both ipsiversive and contraversive saccades. In an inactivation study in the head-unrestrained cat, Goffart and Pélisson (1998) showed that the gaze saccades in the direction of the inactivated FOR (ipsiversive) were hypermetric. This hypermetria was constant across tested gaze amplitudes and resembled the consequence of a systematic shift of the target. In contrast, the gaze saccades in the direction opposite to the inactivated side (contraversive) were hypometric. Moreover, in this case the final error was proportional to the gaze amplitude. The authors suggested that the FOR has a dual role in regards of the gaze direction. (1) In case of ipsiversive saccades, the FOR would influence the visual vector; while (2) in case of contraversive saccades, it would adjust its gain by acting on the transformation from the visual vector to the motor vector.

To sum up, the SC sends a vectorial motor command to the BBG and on a parallel pathway to the NRTP which relays the information to the cerebellum, at the location of the OMV. The OMV sends then inputs to the BBG *via* the caudal fastigial nucleus (also as referred as the FOR). Therefore, the BBG receives descending inputs from the SC and a side-loop signal from the OMV. The premotor saccadic signal issued to the ocular motoneurons are a summation of these two inputs (Iwamoto and Kaku, 2010). This subcortical substrates are involved in the final motor command generation and are common to both RS and VS. In contrast, cortical substrates involved in saccade programming show stronger specialization, with the PEF and the FEF being preferentially involved in reactive and voluntary saccades, respectively (Gaymard et al., 1998a). **This PhD work will focus on RS and VS triggered when exploring a visual scene.**

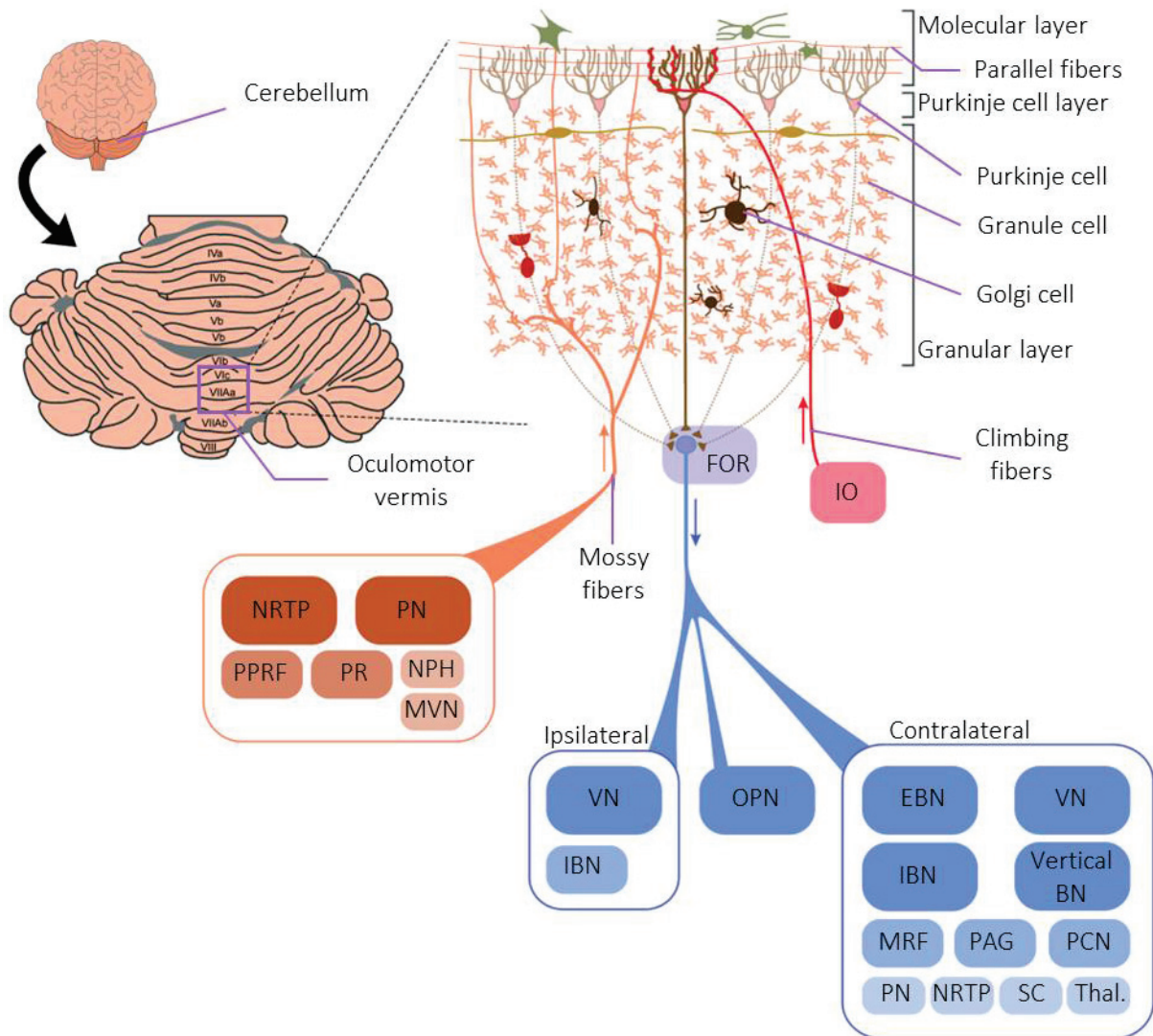


Figure 11: Cerebellum organization at the level of the oculomotor vermis. *Left panel: dorsal view of the cerebellum. Right panel: Anatomical organization of the cerebellar cortex (top). Mossy fibers input the cerebellar cortex and originate from the brainstem (shown in brown). Climbing fibers also input the cerebellar cortex and originate from the Inferior Olive (IO, shown in red). Outputs leave the cerebellum via the Fastigial Oculomotor Region (FOR, shown in blue). Anatomical importance is represented by box relative sizes. NRTP = Nucleus Reticularis Tegmentis Pontis; PN = Pontine Nuclei; PPRF = Paramedian Pontine Reticular Formation; PR = Pontine Raphe; NPH = Nucleus Prepositus Hypoglossi; MVN = Medial Vestibular Nucleus; VN = Vestibular Nuclei; OPN = Omnipause Neuron; EBN / IBN / VBN = Excitatory / Inhibitory / Vertical Burst Neuron; MRF = Mesencephalic Reticular Formation; PAG = Peri-Aqueductal Gray; PCN = Posterior Commissure Nucleus; Thalam. = thalamus; SC = Superior Colliculus (adapted from Prsa and Thier, 2011).*

2. Oculomotor plasticity

2.1. Introduction

2.1.1. Definition of sensorimotor plasticity

Brain plasticity is the ability of the Central Nervous System (CNS) to change. It involves functional and architectural changes at different levels. Plastic changes may reflect in transferring a given function to another brain area, or modulating the grey matter thickness. At the cellular level, plastic changes are thought to take place at the synaptic level and involve, for example, increasing or decreasing synapse number or modulating the synaptic transmission strength. This ability of the system to change is of utmost importance since it allows essential process to happen, such as memory, learning, adaptation, and compensation after injuries. In the sensorimotor framework, plasticity allows to maintain optimal motor behavior in reaction to changes in the body and/or the environment.

2.1.2. Plasticity of eye movements

Eye movements, as any motor behavior, necessitate plasticity to keep optimal performance despite short-term or long-term variations of sensorimotor transformations. Indeed, if these movements were not able to change, the fixation of the target during smooth pursuit or when the body and head move, and the foveation of saccadic target would be less efficient, constantly necessitating corrections. Fortunately, plasticity has been shown to happen in all of these eye movement types: smooth pursuit (Burde et al., 1975; Takagi et al., 2000), vergence (Cooper, 1992), vestibulo-ocular reflexes (Furman et al., 1989) and saccade (McLaughlin, 1967; Abel et al., 1978).

2.2. Saccadic adaptation

In the previous section (1.2) we presented the saccadic system, the model of motor behavior studied in this thesis. We mentioned that saccades are brief and accurate movements. They allow foveation, which make them a critical component of visual perception and any saccadic inaccuracy can result in impaired visual perception (Leigh & Zee, 1999). However, because of their duration (usually less than 50 ms) and because of saccadic suppression, sensory feedbacks are not available before the eyes land on the selected target. Online correction in response to external perturbation is not possible in ordinary conditions¹. Therefore, one might reasonably interrogate how this saccadic precision is achieved. Well, when the system faces repetitive errors, the brain is able to modify the motor command sent to the EOM and thus modulate saccadic amplitude and/or direction. This modulation of the motor command eventually leads to an abolishment of the mismatch between the eyes landing position and the visual

¹ some on-line trajectory control has been reported for large saccades (Gaveau et al., 2003) or for pathologically-slowed saccades (Zee et al., 1976).

target. This mechanism, called Saccadic Adaptation (SA), is gradual and rely on functional and architectural plastic changes at the level of the CNS.

2.2.1. In ecological environment

Munoz et al. (1998) recorded eye movements of individuals aged between 8 and 79 year-old. The saccades were accurate for the entire population. Yet, EOM tonicity and strength change with growth and aging. This study indirectly suggested that the modifications underwent by the EOM are compensated by changes in the motor command they receive.

Along the growth and the aging, one might also consider that we perform up to 200,000 saccades a day (up to 3 per second). If I'd make that amount of steps a day, my leg muscles would be tired. However, EOM are very resistant to fatigue as confirmed by two *in vitro* studies (Frueh et al., 1994; Kaminski and Richmonds, 2002). Furthermore, an *in vivo* study in monkeys (Prsa et al., 2010), showed that saccades elicited by microstimulation of the abducens nucleus before and after a session of more than 300 saccades were identical in velocity and amplitude, arguing for EOM fatigue resistance. However, care must be taken as fatigue does affect saccade kinematic parameters. Indeed, the main sequence, the stereotyped relationship between peak velocity and amplitude, can be modified after the execution of a large amount of saccades (Chen-Harris et al., 2008; Fuchs and Binder, 1983; Golla et al., 2007; Straube et al., 1997; Xu-Wilson et al., 2009a; Xu-Wilson et al., 2009b). This decrease of saccade peak velocity is mainly due to cognitive variables such as motivation or mental fatigue. But saccade accuracy on the other hand is not –or less– affected, the decrease of peak velocity being compensated by an increase of saccade duration. This type of online control of saccades is thought to be controlled by the cerebellum. Indeed, patients with OMV lesions (Golla et al., 2007) or spinocerebellar ataxia (Xu-Wilson et al., 2009a) experiencing this fatigue-induced decrease of peak velocity do not show compensation by saccade duration and therefore, make inaccurate saccades.

2.2.2. In pathology

SA has been observed in patients with monocular paresis which refers to weakness of one or more EOM. Abel et al. (1978) recorded eye movements of a patient with a medial rectus paresis secondary to a partial third nerve palsy. The saccades of the unaffected eye were normometric while the paretic eye performed hypometric saccades. When the unaffected eye was patched for six days, the authors observed that the saccadic gain increased for both eyes until the paretic eye performed normetric saccades (the unaffected eye performed hypermetric saccades). The patch was switched to the paretic eye and the saccadic gain decreased down to normetric saccades for the unaffected eye (and therefore hypometric saccades for the paretic eye). Interestingly, the authors reported that the time needed to increase the gain was longer than the one to decrease, a difference between forward and backward adaptation which will be detailed later. Couple of years earlier, Kommerell et al. (1976) reported similar findings. The two patients they recruited had the interesting particularity that the paretic eye had a better acuity. Accordingly, in these patients, the eye performing normetric saccades was the paretic eye while the unaffected eye was hypermetric.

These two sets of data first suggest that the modulation of the saccadic gain comes from an equal change of nervous input received by the two eyes and not from muscles rehabilitation since when one eye was patched saccade became normometric for the viewing eye but hyper- or hypometric for the non-viewing eye.

Furthermore, the visual feedback seems to be important for this modulation to take place since saccade normometry was always re-established in the eye with strongest visual input, the other eye being patched in Abel et al.'s (1978) study or ambliopic for the patients in Kommerell et al.'s study (1976).

2.2.3. In the laboratory

To induce SA in the laboratory, there are two ways. The first one involves reproducing patients' deficits with invasive interventions and is used with non-human primates. The second can be used with humans and consists in simulating a saccadic aiming error which the CNS will interpret as a need to update the motor command sent to the EOM to satisfy a new sensorimotor transformation. In this latter case, SA is readily induced using two main paradigms: (1) the double-step paradigm and (2) the constant-error paradigm. The saccadic accuracy is evaluated with the gain (see the Amplitude gain section, 1.2.2.1), and the effect of SA is measured by comparing the gain pre- and post-exposure (Figure 12).

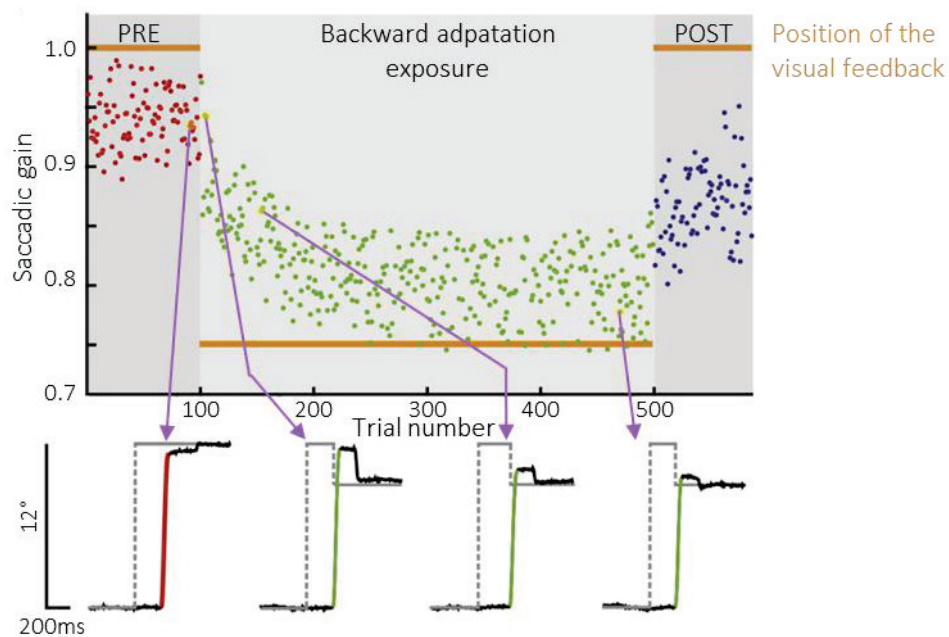


Figure 12: Gain change before, during and after exposure to saccadic adaptation. *PRE:* During the pre-exposure, the baseline gain is measured in a typical saccadic task in which the visual target is extinguished to prevent visual feedback after the saccade. *Backward adaptation exposure:* during the exposure phase, a biased visual feedback is provided, the target is stepped in the opposite direction of the saccade and results in a decrease of the saccadic gain. *POST:* the gain is again measured in the same experimental conditions as the pre-exposure, no visual feedback is provided to avoid de-adaptation. The difference between the pre- and the post-exposure phase, usually expressed in percentage, measures the saccadic adaptation after-effect (adapted from Herman et al., 2013).

2.2.3.1. Paradigms

Invasive induction of saccadic adaptation: please don't try this at home

In 1980, Optican and Robinson performed in monkey a tenectomy of the tendon of the medial and lateral recti of one eye. This surgery resulted in the weakening of the affected eye for saccades in the horizontal plan. After some days of recovery, they recorded movements of both eyes. The unaffected eye performed normometric saccades while the paretic eye performed hypometric saccades. The authors then patched the unaffected eye and after five days, the paretic eye performed normetric saccades while the unaffected eye performed hypermetric saccades (Figure 13). This study was the first to highlight similar adaptive mechanisms among non-human and human primates and allowed to provide a non-human primate model of saccade adaptive mechanisms previously demonstrated in human patients. In addition, another study by Scudder et al. (1998) compared and revealed strong similarities of adaptation characteristics between this invasive procedure and the double-step target procedure detailed below

This invasive protocol was also used in a study reporting the case of non-conjugate SA (Snow et al., 1985). In their study, monkeys underwent tenectomy of one eye. The affected and unaffected eyes were alternatively patched replicating previous results. They then removed the patch and both eyes had access to visual feedback. After 22 to 50 days, normetric saccades were restored for both eyes. This study provided evidence that saccades can be adapted in both conjugate and non-conjugate fashions. **This PhD work will focus on conjugate saccadic adaptation.**

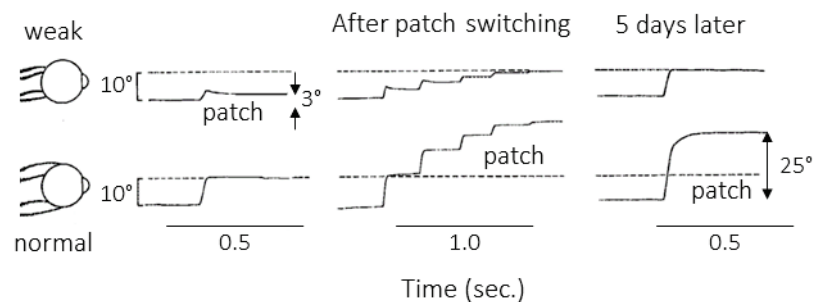


Figure 13: Saccadic adaptation induced by eye weakening in monkeys. A tenectomy was used to mimic a paretic muscle condition in one eye ('weak'). When the unaffected ('normal') eye is viewing, the affected eye produced hypometric saccades (first column of eye position plots). Immediately after switching the patch to the unaffected eye, the monkey performs corrective saccades to reach the target (second column). Finally, after five days, the viewing weakened eye now accurately reaches the target in one saccade, while the unaffected patched eye performs a hypermetric saccade (adapted from Optican and Robinson, 1980).

Double-step paradigm (McLaughlin, 1967)

The double-step paradigm consists in displacing the visual target while the subject is executing a saccade towards it. With the saccadic suppression phenomenon, this intra-saccadic step (ISS) is usually not consciously perceived by subjects and leads to a mismatch between post-saccadic eye fixation and

target location which is interpreted by the CNS as a saccade aiming error. Usually, a short-latency corrective saccade follows and allows the foveation of the stepped target. In this paradigm the ISS is constant relative to the visual target and therefore as the SA takes place and the amplitude of the saccades is modulated, the mismatch between the eyes landing position and the stepped target decreases.

Constant-error paradigm (Robinson et al., 2003)

The main difference between the constant-error paradigm and the double-step paradigm is that in the former, the error is not diminished as SA takes place. Indeed, in the constant-error paradigm, the stepped target is displaced at an eccentricity depending on the eyes landing position and not the initial visual target. This paradigm involves that the target step is consciously perceived by the subject since it occurs at the end of the adapted saccade.

2.2.3.2. Different types of saccadic adaptation

SA paradigms can be tuned in order to adapt saccade amplitude and direction. The directional SA is poorly studied and is not of interest to this work so we will not further develop on that point.

Regarding the amplitude SA, the saccadic gain can be increased (ISS in the same direction of the primary saccade) or decreased (ISS in the opposite direction), SA is thus referred to as **forward** and **backward** respectively. Also, SA can be induced in both modalities of saccades (Figure 14). In the reactive modality, the fixation point suddenly jumps to another position, and subjects are instructed to follow the target as fast as possible. When the RS is detected, the visual scene is shifted. In the voluntary modality, several targets are present on the screen at the beginning of the trial. Subjects are instructed to explore, at their own pace, the visual scene in a given order, with the saccade to-be-adapted at the end of the trial. When this saccade of interest is detected, the entire visual scene is stepped. Although not entirely deciphered, we now know that the different types of SA are underpinned by partially segregated neural substrates which we will develop on later (see for review Pélisson et al., 2010). **In this work, we were interested in backward and forward adaptation of both voluntary and reactive saccade.**

2.2.4. Properties of saccadic adaptation

2.2.4.1. Adaptation time course

In the princeps study of SA, McLaughlin (1967) displayed a first target at 10° of eccentricity which was shifted backwards at 9° of eccentricity. One subject performed this ISS trial eight times. Even though we are in the post replication crisis era, we still can conclude that SA starts as soon as an error is detected by the CNS. Nowadays, the SA paradigm has been replicated hundreds of times and we know that this procedure yields to a progressive, exponential-like, change of saccade gain reaching an asymptote after around 100 trials in humans (Miller et al., 1981) and 1000 in monkeys (Straube et al., 1997) for backward adaptation.

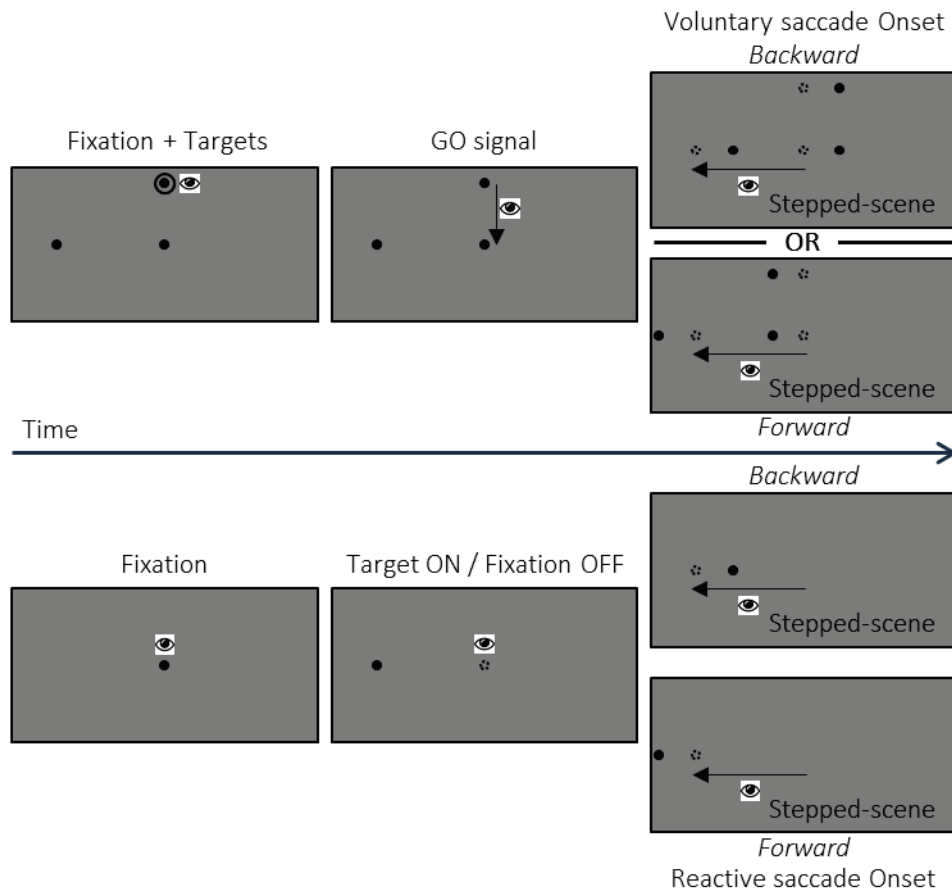


Figure 14: Typical trials for inducing saccadic adaptation. These paradigms were initially introduced by Deubel (1995a). **Upper panel:** Voluntary modality. After the circle around the fixation point turns off, subjects have to make, at their own pace, a downward saccade to the central point and then a horizontal –voluntary– saccade to the peripheral target, the visual scene is shifted backward or forward immediately at the voluntary saccade onset. **Lower panel:** Reactive modality. After a random fixation period, the central dot is turned off while simultaneously, the peripheral target is turned on. Subjects are instructed to initiate a saccade as fast and accurately as possible. The target is shifted backward or forward upon the reactive saccade detection.

Interestingly, when the asymptote is reached, the change in saccadic amplitude does not exactly match the size of the jump (*i.e.* the asymptotic adaptation level is usually less than 75%). The adaptation of RS and VS have a similar time course (Alahyane et al., 2007). After the ISS trials, the retention (or after-effect) of SA is measured using a similar paradigm except that the target, instead of jumping, is turned off, to avoid de-adaptation. The change of gain measured in this post-exposure saccadic task is usually smaller than the one measured in the last ISS trials. The reason is not exactly known but one might think of cognitive strategies that are adding to the plasticity processes *per se*. Finally, if subjects then perform a saccadic task with a visible but no longer jumping target, the gain of the saccades will return eventually to normal. When subjects have undergone a backward SA, the de-adaptation takes longer than the adaptation, while when they have performed a forward adaptation, the de-adaptation is faster (McLaughlin, 1967; Deubel et al., 1986). Since forward adaptation is known to take longer than backward adaptation (Frens and Van Opstal, 1994; Straube et al., 1997; Scudder et al., 1998; Panouillères et al., 2009), these results suggest that rather than being a separate mechanism, de-adaptation is the same process but taking place in the other direction. The difference in speed between forward and backward adaptation has been related to the saccadic system being hypometric at baseline

(Becker, 1989). This hypometric state is advantageous because corrective saccades of the same direction of the primary saccade have shorter latency than those in the opposite direction (that would follow a hypermetric saccade). This particularity of the saccadic system might explain the reason why backward SA is more easily induced than forward SA. Others claimed that the courses of forward and backward adaptation are similar (Albano, 1996; Albano and King, 1989). The different time course usually observed would emerge from difference in the methods. They used an earlier version of Robinson's constant-error paradigm to make their point. Indeed, since the saccades are hypometric, if the backward and forward ISS are of the same size, the error experienced by the system are of different sizes in the two types of SA. Yet, this argument involves that backward adaptation would take longer or be weaker because the error is smaller as compared to forward adaptation.

As stated above, studies using tenectomy to induce SA present data suggesting adaptive changes with time constant over days while here we mention that SA induced non-invasively only takes 1000 trials in monkeys. This raises the legitimate question whether the double-step paradigm truly reveals oculomotor plasticity or cognitive strategies only. A major argument actually supports that non-invasive paradigms can be used to study SA in the laboratory as a model of ecological oculomotor plasticity. Scudder et al. (1998) carefully compared the two methods inducing SA. They suggested that the difference of SA time-course between the double-step paradigm and the tenectomy comes from the fact that the former only adapts one saccadic vector, while the latter requires to adapt all the saccades of the oculomotor range. To test this hypothesis, monkeys first adapted to one saccade vector using the double-step paradigm. The saccade vector was subsequently de-adapted. Then, they underwent the tenectomy and studied the time course of the adaptation of the same saccadic vector. They reported that the two methods led to saccade gain changes following the same time course.

2.2.4.2. Effect on saccade characteristics

Adaptive field

When a given saccadic vector is adapted, it has an impact on other vectors. However, contrary to an initial proposal (Deubel et al., 1996), this impact is not parametric. Short-term SA does not involve a constant shift across the representations of the visual field. The adaptive field, observed in both human and monkeys, describes the oculocentric field of target positions which elicit a modified saccade after adaptation of a single saccadic vector (Albano, 1996; Deubel et al., 1986; Frens and Van Opstal, 1994; Collins et al., 2007a). In short, the closer the tested saccade vector from the adapted saccade vector, the more impacted it is (Figure 15). Vectors which differ by 90° or more are not affected (namely, vertical saccades and saccades in the opposite direction in case of an adapted horizontal vector). The adaptive field is oculocentric, centered on the target position that elicited the adapted saccade (Frens and Van Opstal, 1994). Oblique saccades sharing the same horizontal component with the adapted vector are affected equally for upward or downward saccades. This symmetric organization of the adaptive field does not hold true for the amplitude component, as the larger the saccade the more affected it is (Noto et al., 1999).

Schnier et al. (2010) have shown that the adaptive field of forward SA resembles the adaptive field of backward SA. Finally, the spatial generalization and the adaptation field have been recently extended to voluntary saccades (Alahyane et al., 2007; Alahyane et al., 2008; Collins et al., 2007a).

As Noto et al. (1999) noticed, the adaptive fields look like the shape of movement fields of SRBN recorded in the SC and the FEF.

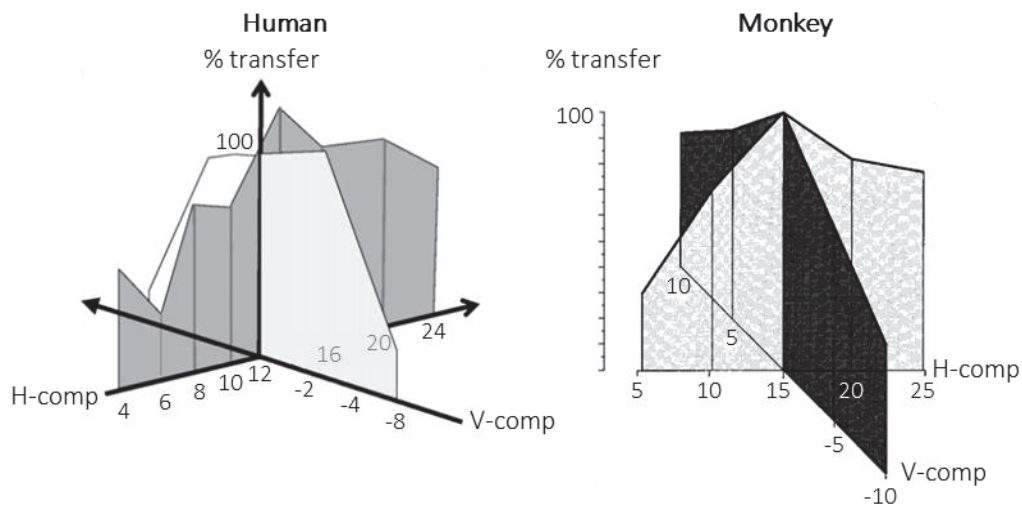


Figure 15: Adaptive fields representing the spatial extent of adaptation transfer from a single horizontal saccade to other saccades. **Left panel:** in human. **Right panel:** in monkey. %transfer is the percentage of transfer (amplitude change relative to the adapted saccade amplitude change) of tested saccades as a function of their horizontal (H-comp) or vertical (V-comp) component (adapted from Collins et al., 2007a for human data and Noto et al., 1999 for non-human primate data).

Saccades kinematics

As already mentioned, saccades are stereotyped movements obeying a predefined main sequence relationship. Yet, SA modifies the amplitude of saccades. The first thing to check is whether this relationship is preserved or not after SA. As simple as this question sounds, the answer is not straightforward, and the literature provides contradictory results. Some authors say no (Alahyane and Pélisson, 2005; Alahyane et al., 2007; Frens and Van Opstal, 1994), some say yes (Zimmermann and Lappe, 2010; Collins et al., 2008; Abrams et al., 1992). For the cons people, their studies report that the modification of saccade amplitude was accompanied by the diminution of the peak velocity and the duration of saccade, thus preserving the main sequence relationship. For the pros people, their results show that adapted and unadapted saccades of the same amplitude have different velocities (Abrams et al., 1992; Zimmermann and Lappe, 2010) or that they differ both in their peak velocity and duration (Collins et al., 2008). However, these studies did not control for fatigue and we saw earlier (see Saccadic adaptation In ecological environment section, 2.2.1) that the main sequence can be modified to oppose the fatigue effect and preserve saccadic accuracy. To disentangle the debate, Ethier et al. (2008a) studied forward and backward adaptation modifications with a protocol allowing to control for fatigue. Subjects performed the saccadic adaptation exposure in a first session. The authors kept track of the saccadic amplitude in each trial. In the second session, subjects were exposed to targets displayed at the endpoint of the saccade performed in the corresponding trial in the previous exposure session. For example, subject A performed a saccade of 10° amplitude in the 27th trial, the next day, the target of the 27th trial was presented at 10° (in fact slightly more than 10° to take into account subject's hypometria). They found that compared with this control session, the forward adaptation session did

not reveal any change in the main sequence. Conversely, for the backward adaptation, the adapted saccades were slower, longer and had reduced peaks of acceleration and deceleration. They suggested that this discrepancy comes from two different mechanisms subtending SA. Forward adaptation would involve a modification of the internal representation of the target while backward adaptation would involve a modification of the internal feedback during the saccade (which therefore involves modification of the dynamic of the adapted saccades). This sounds the end of the debate, however, in their experiment, sessions were separated by one day. Alahyane and Pélisson (2005) reported a significant retention five days after exposure to backward RS adaptation. The saccades elicited in the control session of Ethier et al.'s (2008a) study are into the adaptive field and therefore could possibly be impacted by the adaptation performed the day before. So, this controlled protocol should be replicated but with at least one week between the two sessions to be certain that the control saccades were not affected by transfer.

2.2.4.3. Studies of transfer between different saccade types

As we highlighted earlier, RS and VS rely on partially segregated substrates, especially at the cerebral cortex level (see Neural substrates of saccade production: from the central nervous system to the periphery section, 1.2.6). Thus, studying the transfer of adaptation to different categories of saccade may allow to suggest where the adaptation takes place, either at the sensory level (cortical areas) or at the motor level (downstream subcortical areas) common to both RS and VS. Moreover, it is theoretically possible that adaptation takes place at different levels in the saccadic system. Since this PhD work is about reactive saccades and scanning voluntary saccades, this section will focus only on these two categories.

Deubel (1995a) tested both the transfer of RS adaptation to VS and vice versa. He found that the RS adaptation decreases the gain of VS but this difference did not reach significance. In the other direction he found a small, but significant; transfer of VS adaptation to RS. Later, four studies investigated this directional transfer and found similar results. The four studies reported that RS adaptation transfers to VS (transfer rates: 22% (Alahyane et al., 2007); 57% (Cotti et al., 2007); 12% (Collins and Doré-Mazars, 2006); 36% (Zimmermann and Lappe, 2009)) but this transfer was always weaker than the one of VS adaptation to RS (79%; 75%; 91%; and 43% respectively). The fact that the transfers are not complete suggests that SA takes place at a common site but also at other segregated sites. Moreover, the asymmetry between VS and RS suggests that VS adaptation site would be upstream as compared to the RS adaptation site allowing to have a bigger influence on this later.

And finally, anti-saccades. I know it was supposed to be just about reactive and voluntary scanning saccades but, let me explain. First you may have not noticed but I'm a very talkative ~~writative~~ person. Second, studying the transfer between pro-saccade (the one we have been talking about for approximately 30 pages) and AS is interesting because in the later, the sensory vector and the motor vector are entirely dissociated. Therefore, it is easy to disentangle whether adaptation takes place at a sensory or a motor level. Two studies used this trick to investigate this issue. Levy-Bencheon et al. (2013) adapted leftward AS (which means that the visual target was presented on the right). After the saccade, the target "reappeared" in the landing hemifield. The target was stepped in three different fashions, either at the mirror location of the visual target, or stepped forward during the saccade, or stepped forward 800 ms after the detection of the saccade which is a too long delay to induce adaptation (see below in the Properties of the teaching signal, 2.2.5.1). They then tested the amplitude

of rightward or leftward pro-saccades. The rationale being: if the rightward pro-saccades were affected by transfer of AS adaptation, then the visual vector is adapted, whereas if the leftward pro-saccade were affected, then it is the motor vector which is adapted. The results showed that the leftward pro-saccades had a significant increase in gain after exposure to stepped targets during the AS, but not after the 'mirror' or 'delay' control exposures. However, in this study, the visual feedback was presented in the left hemifield to adapt the AS, therefore, it is difficult to exclude a visual component as acting on this adaptation procedure. Cotti et al. (2009) did the opposite, they adapted pro-saccades in the reactive and voluntary modalities, each time only for one saccade direction. They then tested the transfer to AS in both directions: the adapted one (for which the target appeared in the unadapted hemifield) and the unadapted one (for which the target appeared in the adapted hemifield). After RS adaptation, the saccadic gain was modulated for AS towards the adapted direction but not for AS towards the unadapted hemifield. Conversely, after adaptation of VS, the gain was modulated for both AS in the adapted and unadapted directions. These results suggest that RS takes place at the motor level, whereas VS adaptation would take place at the sensory level.

2.2.4.4. Contextual factors

Eye position

In the adaptive field section (Effect on saccade characteristics, 2.2.4.2), we mentioned the transfer of one adapted vector to other saccadic vectors starting from the same eye position. Here we are interested in the transfer of adaptation to the same vector but with different starting position of the eye. The starting position of the eye can be considered as a spatial cue in the oculocentric space. There are two methods to test this contextual cue.

The first one consists in simply adapting one vector from one starting position and test the same vector but with the eyes starting at different positions. When the adaptation occurs for saccade starting at the center of the subject's oculomotor range, Frens and Van Opstal (1994) and Semmlow et al. (1989) showed that adaptation transfers to saccade starting at other eccentricities. Albano (1996) and Deubel (1995b) showed the same results for adapted saccades starting at more eccentric positions. The story could stop here but Havermann et al. (2011), while confirming these results for saccade starting positions at the center, showed that when adaptation is induced for saccade at $\pm 10^\circ$ the transfer decreases with the distance from that starting position. Finally, Zimmermann and Lappe (2011a) showed that forward adaptation of both RS and VS are affected by eye position with VS being more sensitive to this contextual cue.

The second method to test this contextual cue is to simultaneously adapt the same vector starting from different eye position with different types of adaptation, namely backward and forward. If the eye position is not a cue, the gain change should be nullified by the two opposite exposures. The studies testing that approach showed that both backward and forward adaptation took place indicating that when the saccadic system is submitted to contradictory demands, the eye position can be taken as a contextual cue (Aboukhalil et al., 2004; Alahyane and Pélisson, 2004; Semmlow et al., 1989; Shelhamer and Clendaniel, 2002; Shelhamer et al., 2005; Tian and Zee, 2010).

Visual properties of the saccadic target

Using the approach of adapting the same vector, Bahcall and Kowler (2000) presented squared targets with a forward ISS while diamond targets elicited a backward ISS. They did not highlight significant gain modulation. Deubel (1995b) also failed to highlight an effect of the visual properties of the saccadic target. However, Herman et al. (2009) did highlight a modulation of gain in the two different directions with gain decrease for a flickering target and gain increase for a steady target. The difference between Herman et al.'s (2009) study and the first two studies presented is that, in the former, the different targets were presented in different blocs. Maybe this temporal dissociation reinforced the contextual cue. Other contextual cues have been shown to impact SA such as target distance (Chaturvedi and Van Gisbergen, 1997), and head orientation (Shelhamer and Clendaniel, 2002).

To conclude, the saccadic system is able to use contextual factors in SA or not depending on their relevance.

2.2.4.5. Short-term and long-term adaptation

Since the earliest investigations, SA has been suggested to follow two different time scales, likely corresponding to different processes. Indeed, Miller et al. (1981) already proposed a short-term and a long-term process. They further suggested that the double-step paradigm only engaged the short-term process. Although the idea of two time scales has been retained, the conclusion that the double-step paradigm only engaged short-term adaptive processes has been challenged. Indeed, Alahyane and Pélisson (2005) conducted a study in which subjects performed one exposure of backward adaptation of RS and test the retention of this exposure for 19 days. They highlighted that there was a significant retention up to five days after the exposure. These results involve that both short-term and long-term processes take place during the double-step paradigm. To engage long-term adaptive processes, Robinson et al. (2006) studied monkeys performing the double-step paradigm on 19 consecutive days. They compared the gain of saccades before the adaptation exposure of each day. The gain before the exposure phase was smaller on the following day arguing for a retention effect. However, the gain measured before the exposure process was bigger than the gain measured at the end of the exposure of the day before, arguing that the retention was not complete. Moreover, on the last day, the decrease of the gain during the exposure session was bigger than on the first day.

An interesting approach was used by Kojima et al. (2004). They induced forward adaptation then de-adapted up to restore the normal gain and then re-induced forward adaptation. They also tested with backward adaptation. They found that for both forward and backward adaptation, the gain changed faster in the second exposure (after de-adaptation) than during the first exposure. This suggests that a memory trace is kept by the saccadic system to facilitate subsequent adaptation. This memory trace could be the signature of a long-term process which has not been canceled by the de-adaptation exposure engaging a short-term adaptive process. To test the hypothesis that this memory trace is specific to the saccadic system, Kojima et al. (2004) adapted horizontal saccades and tested horizontal, vertical, and oblique saccades. The results showed that only the horizontal component was affected by the memory trace arguing for plasticity of this meta-learning at a specific site in the saccadic circuitry. Finally, Ethier et al. (2008b) confirmed the existence of a fast learning system very sensitive to error but labile and a slow system less sensitive to error but more robust to time.

2.2.5. Teaching signal inducing saccadic adaptation

The adaptive modulation of saccadic amplitude occurs in response to a repetitive mismatch between the saccade landing position and the target position. This error signal could hypothetically be of different nature, either sensory or motor. In the following section, we will first expose the properties of the error signal and then discuss its nature.

2.2.5.1. Properties of the teaching signal

Temporal properties

There are two important temporal properties to consider: when and how long should the error be presented to induce SA.

First, when: namely the critical period of presentation. To test for that, authors introduced a delay between the landing of the saccade and the stepped-target appearance. In monkeys, Shafer et al. (2000) showed that a delay of 750 ms between the end of the saccade and the target appearance still lead to adaptation. However, the adaptation rate was weak. In human, this delay is even shorter. The target must be presented before 600 ms after the saccade landing to elicit some amount of adaptation (Bahcall and Kowler, 2000; Fujita et al., 2002). Noteworthy, these studies emphasize that the target step producing the error signal can be perceived consciously and still induce SA.

Second, how long: namely the period during which the error signal must be available for the system to induce SA. In monkeys, Shafer et al. (2000) showed that the error signal must be available at least for 80 to 100 ms. In humans, Panouillères et al. (2011) showed that this minimal presenting time depends on the saccade type. RS adaptation necessitates the error signal to be present for as short as 15 ms while VS adaptation requires the error signal to be present for at least 50 ms. Even shorter durations have been disclosed for RS by Panouillères et al. (2013b).

Visual properties

The error signal is usually induced by small targets in a poor environment, *i.e.* in laboratory conditions (not that I am complaining...). Therefore, a set of studies have investigated the optimal visual properties for a target to induce an error signal. Bahcall and Kowler (2000) have shown that a target of 3° (compared to the 0.5° targets usually used in SA) can elicit SA. Also, Collins et al. (2007b) have shown that a string of letters can induced SA. Finally, in their study, Bosco et al. (2015) managed to adapt saccades towards bars that did not jump. The bars were shortened by the more eccentric edge (the less eccentric edge remains at the same eccentricity). These results suggest that the saccadic system uses the center of gravity of selected objects for computing the error signal.

The effect of the visual background has been studied and found not to influence backward (Robinson et al., 2000) nor forward adaptation (Ditterich et al., 2000a).

Finally, the presence of distractors during SA was tested. In this protocol, the saccade target could be either a red circle or a yellow square. The saccade was elicited by one of these shapes randomly. During the saccade, the other shape was displayed and acted as a distractor (Madelain et al., 2010). The authors

highlighted that gain modulation occurred only when the step was made by the target and not the distractor. This study suggests that the error is selective regarding the pre-selected target.

Size of the intra-saccadic step

Studies have shown that the manipulation of the ISS size can modulate the strength of the adaptation. It has been shown that an ISS as small as 0.25° (for a primary saccade of 10°) can induce SA (Herman et al., 2013). In their study, Robinson et al. (2003) showed that the optimal ISS amplitude depends on the size of the first target step (*i.e.* the amplitude of saccade before the adaptation). They conclude that SA was the strongest for errors between 15-45% of the primary saccadic step. In monkeys also, increasing the ISS leads to decrease the adaptation strength (Straube et al., 1997).

Finally, the saccadic system is also sensitive to the consistency of the ISS. In Havermann and Lappe's (2010) study, subjects performed alternatively forward and backward adaptation. The average error was kept constant but the noise in the ISS step was varied. As the distribution of the ISS size around the mean became larger, the SA became weaker. They concluded that the saccadic system needs to encounter a consistent, coherent, error to correct for it. This conclusion seems to contradict a study of Srimal et al. (2008). In their study, the ISS was randomly backward or forward. A trial-by-trial analysis highlighted that the gain of the n^{th} trial was modulated by the error of the experienced at $n-1^{\text{th}}$ trial. This result implies that the consistency of the error is not necessary. However, in this study, long sequences of either backward or forward step happened. Therefore, the trial-by-trial gain modulation their results led them to conclude, after modeling their data, might have arisen from these periods of subsequent trials with ISS in the same direction. Moreover, the apparent contradiction of these two studies might be due to the co-existence of two different mechanisms with the trial-by-trial correction used in the SA process.

2.2.5.2. Nature of the error signal

The properties of error signals presented above allow to unravel their nature, motor or sensory.

Motor hypothesis

When the primary saccade does not land accurately on the target, a corrective saccade usually follows. The motor command allowing this correction was suggested to provide the error signal which would therefore be of a motor nature. The simplest way to test for this is to try to abolish the corrective saccades and measure the adaptation rate. If the adaptation rates were similar with and without corrective saccades, then the error signal does not emerge from this motor command. Easier said than done, however, by modifying the double step paradigm, some authors have managed to do so in monkeys (Wallman and Fuchs, 1998; Noto and Robinson, 2001) and in human (Wallman and Fuchs, 1998; Bahcall and Kowler, 2000). To abolish the corrective saccades these studies used different strategies. First Noto and Robinson (2001) extinguished the stepped target 90 ms after the deceleration of the saccade was detected. In their results, they reported that in the conventional paradigm, every saccade was followed by a corrective saccade (around 1000 trials). In the modified paradigm, only 2% of the saccades were followed by a corrective saccade. The amount of percentage gain change achieved in the two different paradigms was similar. Wallman and Fuchs (1998) used another trick to test the motor error hypothesis. In their study, the backward stepped target was briefly presented at the end of the saccade. Before the corrective saccade occurrence, the target was displaced again back to its initial

position. This paradigm resulted in replacing the usual backward corrective saccade observed in backward adaptation by a forward corrective saccade since the primary saccade was hypometric. Despite a forward motor error, the saccadic gain decreased gradually. The investigators also tested two human subjects performing this paradigm and found similar results. Finally, recall that in their study of the effect of the target size, Bahcall and Kowler (2000) showed that target size does not impair SA. However, the size of target did impair the production of corrective saccades: the bigger the target, the lesser the number of corrective saccades (see Kowler et al., 1995 for similar results). Therefore, this set of studies points away from the motor error hypothesis.

Retinal error hypothesis

Rejecting the motor error hypothesis, Noto and Robinson (2001) and Wallman and Fuchs (1998) logically proposed a visual hypothesis where the error signal emerges from the retinal difference between the landing position and the target. However, a set of studies highlighted discrepancies between this hypothesis and the data reported by these studies. In one of their experiments Bahcall and Kowler (2000) tested the effect of the retinal offset on adaptation. To do so, they asked subjects to make a saccade representing 75% of the size of the first target step, which they did accurately in a session with no target steps. In the backward exposure session, the target was stepped by around 20%. Therefore, when the saccades with a 75% intended gain landed, the retinal error was in a forward direction. However, the gain decreased gradually, departing from the hypothesis of the forward retinal error causing adaptation. Large saccades have a tendency to undershoot more than small saccades (Becker, 1989). Bonnetblanc and Baraduc (2007) suggested that these large saccades can be adapted with no visual feedback. In their study, they asked subjects to perform saccades towards a 34° eccentricity target. In one condition the target remained on the screen allowing a corrective saccade to accurately foveate the target. In another condition, the target was turned off during the saccade so that no corrective saccades were elicited. However, after 75 trials, the gain of these saccades increased to reach the same final position as the primary saccade plus the corrective saccades in the condition with the visual feedback. Therefore, this study provided evidence that the saccadic system does not need visual feedback and that retinal error is not necessary to induce adaptive changes. In the same vein, in Panouillères et al. 's (2013b) study, SA was induced with the target stepped during the saccade and blanked at the landing. This study is interesting for two points: (1) it provides further evidence that the retinal post-saccadic feedback is not necessary and (2) that visual information has been integrated during the saccade, challenging the hypothesis of the saccadic suppression phenomena. Herman et al. (2013) also tested the retinal error hypothesis serendipitously in a study designed to determine the minimal ISS size needed to induce SA. They tested 0 to 1° ISS sizes for 10° saccades. All targets elicited SA and the same proportion of SA was achieved for all ISS sizes. These authors claimed that *'if adaptation halted once a retinal error goal was reached, the proportion of SA achieved would increase with ISS'*. However, this conclusion is not that straightforward, as one might argue instead that the saccadic system is tuned such that the motor commands match a certain percentage of the retinal error and not an absolute retinal error value. Another study argues against the retinal error hypothesis (Havermann and Lappe, 2010). In this study, subjects performed different adaptation with ISS calculated from the landing position of the eye (Robinson's paradigm). They tested several mean eccentricities with several consistency of the ISS size. One of their conditions is of interest for the current matter: the foveal-clamped ISS with 0°SD. In this condition, the retinal error is always null, however, the saccadic system is used to a positive retinal error since saccades are hypometric. In this case, the saccadic system should

interpret this visual feedback as a consequence of a hypermetric saccade and therefore lead to gain decrease. However, results across subjects were not consistent and no such conclusion could be drawn.

Prediction error hypothesis

Well, if neither the motor error nor the retinal error drive adaptation, then what does? Miller et al. (1981) already suggested that the error signal driving adaptation could emerge from a comparison between the prediction of the error and the actual error (the visual consequences of the movement) (Figure 16). The actual visual consequences consist of the retinal image after the saccade lands, and the prediction is the hypothetical image that should input on our retina based on the size and direction of the planned saccade. Mismatch between these two images results in an error that can drive the adaptation up to the point that the actual consequences comply with the predicted image. It can also interestingly be suggested that the system can adaptively become more tolerant about this discrepancy. This could account for the fact that short-term SA does not entirely abolish the mismatch between the eyes landing and the ISS. This hypothesis fits well with the studies presented in the former paragraph. Moreover, Wong and Shelhamer (2011) studied SA with an backward ISS smaller than the expected hypometria: in this case, if the retinal error was used to drive adaptation, gain should increase since the sight fell short of the stepped target. Yet, they reported that the gain decreased because the predicted consequences of the saccade was the target being more undershot than what the retinal error actually experienced.

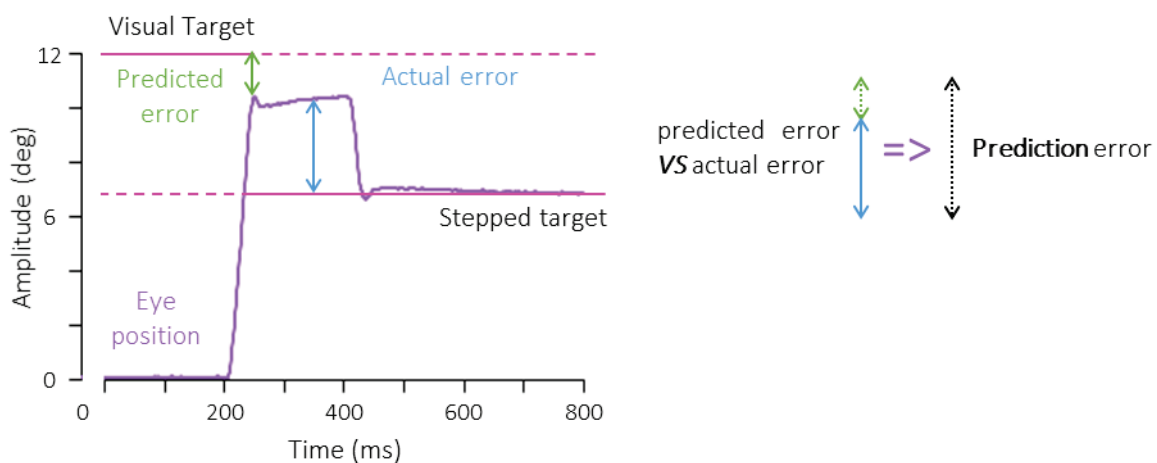


Figure 16: Prediction error hypothesis. The error signal, called prediction error (black double arrow) emerges from the comparison of the predicted error using the corollary discharge (green double arrow) with actual error the system experienced at the end of the movement (blue double arrow).

Actually such prediction error is allowed by the corollary discharge which is known to be accurate enough to estimate the landing position in relation to the target location (Collins et al., 2009). Moreover, these authors showed that after adaptation the CD still accurately conveys the motor (adapted) vector rather than the sensory vector. These results were confirmed by Panouillères et al. (2012b) who used a task involving a sequence of two memorized saccades. Using backward adaptation they modified the amplitude of the first saccade. They tested both RS and VS. The rationale was that if the CD of the first

adapted saccade has been modified according to the motor vector, the second saccade should compensate and land accurately on the second target. Conversely, if the CD encodes the sensory vector, the second saccade should land short by an amount similar to the adaptive reduction of the amplitude of the first saccade. They reported that the second saccade was accurate for both RS and VS and therefore concluded that the CD relates to the motor vector and is adapted simultaneously with the actual saccade.

2.2.6. Neural substrates of saccadic adaptation

2.2.6.1. The cerebellum: when the sidewalk shapes the road

As we mentioned earlier, the cerebellum is involved in the online control of saccadic amplitude. Therefore, it is reasonable to think that the cerebellum can also play a role in short-term adaptation and maybe in long-term adaptation.

Lesion and Inactivation studies (in monkeys)

One short way to test the involvement of a structure in a given process is to test whether this process is preserved after the removal or inactivation of this structure. Taking the first option, early work of Optican and Robinson (1980) has provided strong evidence for the cerebellum involvement in SA. The monkeys were cerebellectomized and the patch on the unaffected eyes was switched to the affected eye. If SA would have occurred, a normal gain of the unaffected eye should have been restored. However, the saccades remained hypermetric even 2 to 4 months after. Takagi et al. (1998) restricted the lesion to the OMV. They reported that out of their three operated monkeys, one had permanently lost the short-term adaptation ability while another one had a transient impairment.

The inactivation procedure has been also extensively used to provide evidence for the cerebellum involvement in SA. This procedure has the great advantage to be reversible and therefore allows finer conclusions. Robinson et al. (2002) inactivated the right and left FOR with muscimol (a GABA_A receptor agonist). Rightward and leftward saccades were hypermetric. After more than 1200 trials the saccades still overshoot. The monkey was then placed in the dark for a 10-hour nap, the time for the muscimol to dissipate. They then tested rightward and leftward saccades which were now, hypometric! Magic you would tell me, but I would say 'no!'. Here is why: the error signal experienced before the *little* nap, produced plasticity which was not translated into saccadic amplitude modulation while the FOR was inactive; however, after dissipation of muscimol effects, such plasticity resulted in the observed reduction of saccadic amplitude. Therefore, it can be concluded that SA takes place upstream of the FOR. Following on their findings, Robinson and colleagues (2005, in Iwamoto and Kaku, 2010) then decided to inactivate the left OMV which resulted in leftward hypometric saccades. After performing 1000 saccades, they were still hypometric. The monkey was again allowed a 10-hour nap in the dark. After muscimol dissipation, the monkey was tested and this time, the gain was still hypometric. Finally, in another experiment, the muscimol inactivating the left OMV was injected right after the backward adaptation of rightward and leftward saccades induced by the target double-step paradigm. After the usual nap, the monkey was tested for saccades in both directions. The leftward saccades were not

adapted anymore while the rightward saccades were. They therefore concluded that the OMV is necessary for occurrence and retention of SA.

Unit recording studies (still in monkeys)

A longer way to investigate cerebellar involvement in SA is to record neurons during the exposure and try to link their activity to the observed changes in saccadic kinematic.

Let's start with the FOR where things are simpler. In the FOR, the typical neuronal activity relates to an early burst of spikes which is correlated with the onset of contraversive saccades while a late burst of spikes correlated with the offset of ipsiversive saccades. The FOR exerts a suppressive action on ipsiversive saccades and their amplitude whereas it exerts a facilitating action on contraversive saccade amplitude. Scudder and McGee (2003) recorded neurons of the FOR before and after weakening of one eye. They were able to investigate forward and backward adaptation by switching the patch from the affected and unaffected eyes. The discharges of the FOR neurons changed in some parameters. The number of spikes associated with contraversive saccades positively correlated with contraversive saccade amplitude which thus both increased after forward adaptation. They concluded that these changes were appropriate to cause adaptive change in amplitude. Inaba et al. (2003) recorded neurons of the FOR during the double-step paradigm. The gain decrease was accompanied by a significant increase in spike discharge; while the gain increase was accompanied by a significant reduction in discharge. All outputs of the OMV leave the cerebellum by the FOR. Therefore, this nucleus activity might reflect processing happening in the cerebellum itself.

Well before I was born but still some 20 centuries after JC, Marr (1969) and Albus (1971) postulated a major role of the cerebellum in motor adaptation. The Purkinje cells receive inputs from the climbing fibers and the mossy fibers. The complex-spike (CS) and the simple-spike (SS) activities rely respectively on these two inputs. According to the Marr-Albus hypothesis, the climbing fibers send information about motor errors and modify the CS activity. The synaptic strength between the parallel fibers and the Purkinje cells is modified and the SS activity is changed in turn. The SS activity is transmitted through the deep nuclei to the cerebellar-recipient structures which, in the case of the saccadic system, could be responsive for changes in saccadic amplitude through modulation of the BBG. To test Marr-Albus' prediction, one has to show that CS activity encodes the saccadic error and that the SS activity is modified during adaptation.

In relation to the first question concerning CS activity, Catz et al. (2005) observed no modulation of the Purkinje cells at the beginning of adaptation when the error is the biggest but only at the end of the adaptation when the error is nearly nullified. Soetedjo and Fuchs (2006) also recorded Purkinje cells in the OMV and highlighted CS activity modulation during the error interval. Interestingly these Purkinje cells had a preferred error direction and the CS discharge did modulate when the error size decreased with saccade amplitude changes. This involvement of CS discharge in error encoding was later confirmed by Soetedjo et al. (2008). Given that CS activity is determined by the climbing fibers emerging from the inferior olive, the information about the error might come from the SC *via* the IO (Prsa and Thier, 2011).

In relation to the second question concerning the SS activity, we know that, at the population level SS activity correlates with saccade duration and amplitude (Thier et al., 2000; Catz et al., 2008): the longer the population response, the longer the saccade duration and therefore the bigger the amplitude (because they are linked by the main sequence). Indeed, the end of the saccade is tightly linked to the

end of the burst of SS population (Catz et al. 2008; Kojima et al. 2010). During forward adaptation SS activity is added at the end of the saccade for it to last longer. During backward adaptation, the decrease of saccadic amplitude results in a reduced peak velocity uncompensated by burst duration (contrary to the increased burst duration maintaining saccadic amplitude observed during fatigue). The amplitude of the saccade, linked by the main sequence to the peak velocity, is thus reduced. In conclusion, during forward adaptation, the correlation between population burst end and saccade amplitude remains while during backward adaptation, it is decoupled.

Cerebellar affections of human patients

Many studies report that the cerebellum has a significant impact on human SA process (*e.g.* Straube et al., 2001; Golla et al., 2007) (see also the princeps study of Optican and Robinson 1980 in the monkey). Waespe and Baumgartner (1992) investigated backward RS adaptation in patients with Wallenberg's lateral medullary syndrome. Their ability to adapt was impaired as compared to control subjects (but see Choi et al., 2008). Waespe and Müller-Meisser (1996) also reported that patients at a chronic stage after a superior cerebellar artery infarction had saccadic dysmetria, implying that they were not able to readjust their saccades thanks to adaptive processes. Furthermore, Xu-Wilson et al. (2009a) showed that cortical cerebellar lesions impact the short-term adaptation and also, albeit to a lesser extent, the long-term adaptation. Alahyane et al. (2008) highlighted in two patients a double dissociation between RS and VS backward adaptation. Indeed, the patient with a medial cerebellar lesion was impaired only for RS adaptation whereas the patient with a lateral lesion was impaired in VS adaptation only. Finally, Golla et al. (2007) showed a partial dissociation between backward and forward adaptation. Their patients had a lesion at the level of the vermis. They reported that backward adaptation was partially preserved whereas forward adaptation was totally abolished

Imagery studies in healthy humans

There are several techniques to non-invasively investigate the role of cerebellar and cerebral structures. Positron Emission Tomography (PET) measures the degradation of radioactive products injected in subjects. For brain imaging, using products that fixate on glucose allow us to infer the activity of cortical cells using glucose for their energy supply. Using PET, Desmurget and colleagues have highlighted an implication of the medio-posterior cerebellum in the backward and forward adaptation of RS (Desmurget et al., 1998; Desmurget et al., 2000) (Figure 17).

It is also possible to follow the Blood Oxygen Level Dependent (BOLD) activity of brain regions with Magnetic Resonance Imaging (MRI) and infer that these regions need more oxygen because they are activated (functional MRI – fMRI). Using this technique, a first study was interested in the processing of the error signal (van Broekhoven et al., 2009). There were two conditions, one for which the target reappeared at the same initial position and another condition in which the target jumped either forward or backward randomly (to prevent saccadic adaptation to take place). The authors reported an activation in lobule VII of the vermis, a bilateral activation in lobules VIII, IX and X and a unilateral activation in lobule VIIb. Also using fMRI, Liem et al. (2013) investigated the error signal processing and reported that the OMV was involved with a bilateral activation of lobules VI, VIII and IX as well as a left unilateral activation of Crus 1 and 2, and lobule VIIb. Furthermore, they had either small or large steps and the results showed that the activation was greater for larger steps. Finally, they also reported that in the OMV the activity was greater for forward than backward steps. Gerardin et al. (2012) investigated

backward adaptation of both leftward VS and RS. Their results revealed an activation of the ipsilateral lobules VIIb and VIII. Conversely, Blurton et al. (2012) did not find activity modulation of the cerebellum that they could link to backward RS adaptation. This discrepancy might be due to their control condition which was different. In Gerardin et al.'s (2012) study, the control condition was a ISS after a delay of 800 ms that is known to induce no adaptation whereas in Blurton et al.'s (2012) study, the delay was only 300 ms which is still within the range that can induce adaptation (see the Temporal properties section of the Properties of the teaching signal 2.2.5.1). Therefore, when contrasting their control condition and their SA condition, the cerebellum activation might have decreased to levels undetectable by fMRI.

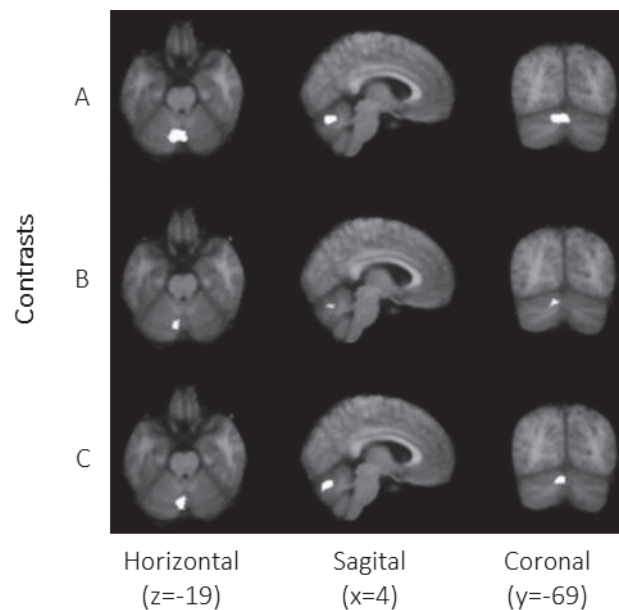


Figure 17: Metabolic modulation of the oculomotor vermis induced by target jumps. The rows represent mean difference images obtained after correction for multiple comparisons for the different contrasts: **A:** between the condition with a consistent (either forward or backward) jump and the one with a random jump; **B:** between the condition with a forward jump and the one with no jump; **C:** between the condition with a consistent (either forward or backward) jump and the one with no jump.

TMS studies in healthy humans

The Transcranial Magnetic Stimulation (TMS) is a technique that sends magnetic shocks to a targeted cortical area. It allows to link causally the targeted area with the investigated process because it either inhibits (frequency of shocks < 1Hz) or facilitates (frequency > 5Hz) its activity. Jenkinson and Miall (2010) targeted the medio-posterior cerebellar cortex with low-frequency repetitive TMS while subjects performed a double-step paradigm inducing backward RS adaptation. They reported that the modulation of saccadic gain related to the adaptation procedure was significantly reduced in the rTMS condition compared to the control (no TMS) condition. Panouillères et al. (2012a) used another TMS approach: the single pulse TMS (spTMS) which is known to disrupt the processing of the target area for a narrow time period (of the order of tens of ms). They tested different timings synchronized to the detection of the saccade: 0 ms, 30 ms, and 60 ms. The shocks were applied on the right Crus 1. First, they found that spTMS shocks delivered at the initiation of the saccades during the pre-exposure phase (with no ISS) disrupted their accuracy. Second, irrespective of their timings, shocks applied during the

adaptation exposure phase differently affected the two types of adaptation: the forward adaptation was facilitated whereas the backward adaptation was impaired.

2.2.6.2. Nucleus reticularis tegmenti pontis

The NRTP receives inputs from the SC as already mentioned (see Subcortical areas section, 1.2.6.2). It projects in turn through the mossy fiber system to the OMV and the FOR (Noda et al., 1990). However, despite this central position in the saccadic system and its control, the NRTP has not received that much attention in SA investigations. To our knowledge, only one study recorded neurons in the NRTP during both forward and backward adaptation (Takeichi et al., 2005). In half of the neurons they recorded, the number of spikes in the burst increased during amplitude decreases. During forward adaptation, none of the recorded neurons had significant activity modulation. These results are difficult to interpret and the sparse data on the role of the NRTP in SA do not allow to draw any conclusion about its involvement in the processing as an integrator or relay of the information.

2.2.6.3. The superior colliculus

The SC is also a major crossroad in the saccadic system since it receives inputs from all cerebral areas involved in the production of saccades. It is also a structure which participates in the transformation of the sensory vector into the motor vector. Therefore, its investigation is interesting regarding the level where SA takes place: motor or sensory. Frens and Van Opstal (1997) have recorded saccade-related burst neurons in the deep layers of the SC. Once they determined their movement fields, they reduced the amplitude of this optimal saccade vector through a double-step adaptation procedure. They reported that the burst of the SRBN did not change after the adaptation even though the amplitude was reduced (see Quessy et al., 2010 for similar results detailed in Figure 18). They concluded that the SC codes for the desired and not the actual movement (Figure 18).

Another interesting approach consists in adapting saccades elicited by microstimulation of the SRBN (Melis and van Gisbergen, 1996). To do so, they electrically elicited saccades in the dark and presented, at the time of saccade termination, a visual target located either slightly forward or slightly backward from the saccade endpoint. They showed that saccadic gain was modulated significantly as in a classical behavioral double-step paradigm. They concluded that SA occurs downstream to the SC and that SA does not involve remapping of the visual world since these saccades were elicited without visual inputs. One can argue, however that these saccades are not physiological and therefore it is possible that the adaptation they highlighted is indeed purely motor but that in physiological conditions, SA would also involve, at least partially, structures upstream to SC. Indeed, this suggested difference between the two adaptation procedures is supported by the fact that the adaptation of the electrically-evoked saccades did not transfer entirely to RS of the same vector. Furthermore, as already mentioned, there might be multiple sites of SA. Conversely, Edelman and Goldberg (2002), found that the adaptation of RS transfers to electrically elicited saccades. The difference between these two studies lies in the current intensities they used to elicit saccades and therefore to resolve this contradiction, it would be interesting to vary both the site and the strength of the stimulations.

Finally, Takeichi et al. (2007) recorded SRBN during SA. This latter was associated with significant modulation either in the number of spikes of the burst or in the shape of the movement field in the majority of the neurons they tested. The changes occurred gradually during SA. In contrast they found

no evidence of any change of active locus on the SC motor map. Nonetheless, they concluded that the site for saccade adaptation is at the level of the SC or upstream.

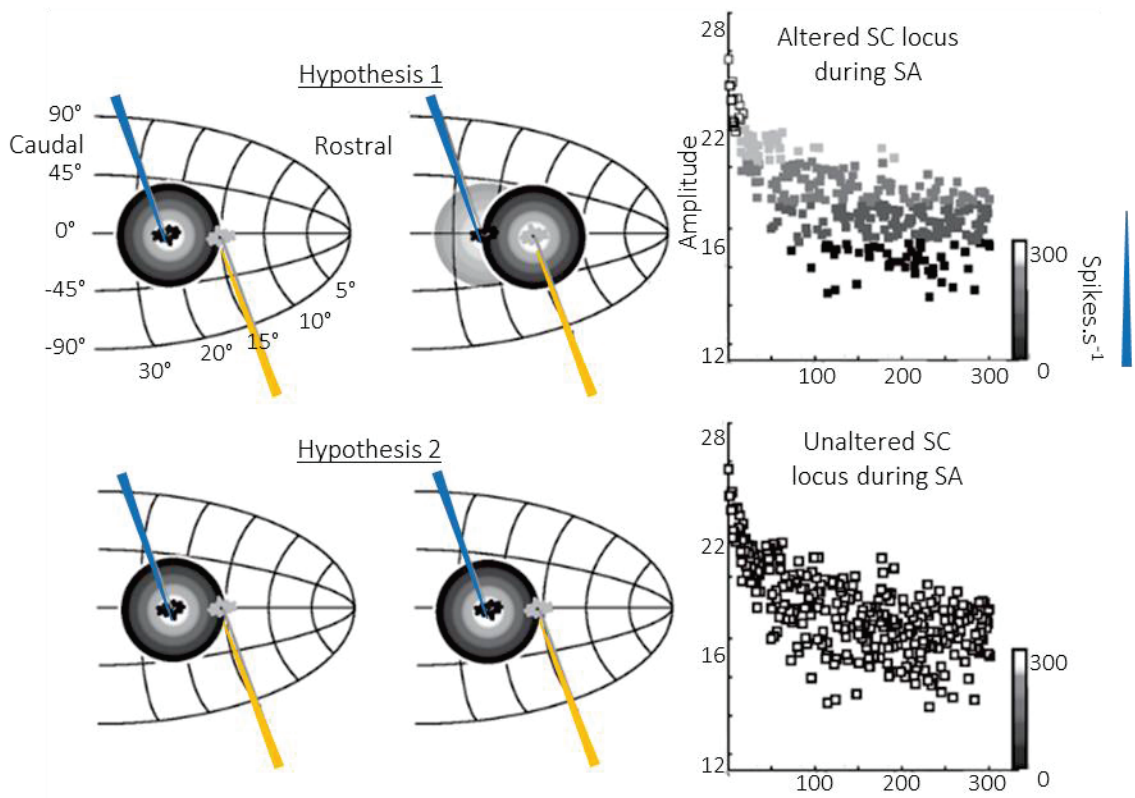
Figure 18: SC hypotheses tested in Quessy et al., (2010) (Next page). Motor activity on the SC map is presented as concentric circles (highest activity represented in white; low activity represented in black). During a 25° horizontal saccadic movement, electrode 1 is located at the population center and electrode 2 is located at the rostral edge of the population. **Hypothesis 1** posits a change in the locus of SC activity during adaptation. This is indicated in the **middle panel**. If activity were recorded from a cell at electrode 1 position, at the start of adaptation discharge rates would be high. This is shown in the **right-most panel** that plots saccade amplitude as a function of the number of adaptation trials and the shading of points indicates the discharge rate (spikes.s⁻¹) of a hypothetical cell. Early in adaptation the cell is at the center of the active population and discharges vigorously. As movement amplitudes decline the active population is presumed to move to more rostral sites and activity is predicted to decline. **Hypothesis 2** predicts no change in location of the active population in the SC. The recorded neuron (electrode 1) remains at the center of the active population throughout the adaptation process. Thus at the end of adaptation, movements that are much smaller than control movements to initial visual target are associated with high discharge rates. In the **two lower panels**, the predictions of these two alternative hypotheses are presented for forward adaptation (adapted from Quessy et al., 2010).

2.2.6.4. Cerebral cortical areas: the surprising outsiders

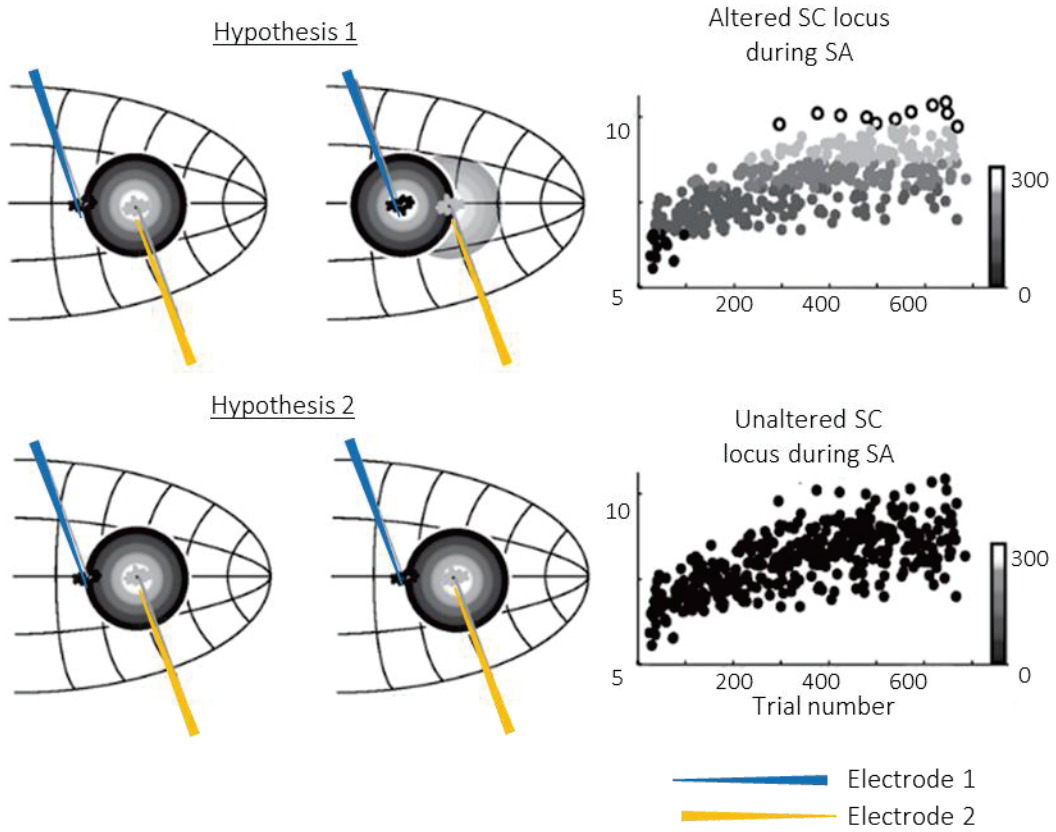
Considering the large extent of the literature investigating the neural substrates of SA which concluded that SA is probably happening at the, common, motor level, it seems unlikely that the cerebral cortex takes a critical part into SA processes. However, as we already mentioned, studies reporting partial and asymmetrical transfer of SA between different saccade types and reporting effects of context hint that the cerebral cortex might have a partial role in SA. Moreover, as we will see in the section Oculomotor space and spatial cognition (section 4), a role of the cerebral cortex is necessary to encompass the effects of SA on localization and visuospatial attention. Furthermore, the cerebellum has projections towards the cerebral cortex *via* the thalamus, and this pathway has been causally involved in SA in a study with patients (Gaymard et al., 2001). In this study, Gaymard and colleagues tested two types of patients. The four patients had focal lesions of the thalamus, however only two of them had a cerebellar syndrome associated with the thalamic lesion. The four patients had normal saccades, as compared to control subjects, implying that the online control of saccade amplitude is not impaired. However, the two patients with the cerebellar syndrome had a partial deficit in short-term SA (SA deficit confirmed in a case-study in a patient with a lesion in the posterior ventrolateral thalamic nucleus: Zimmermann et al., 2015). Finally, studies have reported modulation of the cerebral cortex activity during SA as we will review now.

First, Blurton et al. (2012) used fMRI to test the role of the cerebral cortex in backward adaptation of RS. They reported that the contralateral SEF BOLD signal decreased when the saccadic gain decreased. The SEF SA-related activity was interpreted as a signature of the incorporation of the vestibular information because this area can use different reference frames (Tehovnik et al., 1998; Martinez-Trujillo et al., 2004). The SEF possesses the characteristics to link head, trunk or eye movements using vestibular information and eye-centered coordinates. The study also reports posterior insula activation which has been proposed as a substrate for visual-vestibular interactions (Brandt et al., 2002). For these authors the activations of the SEF and the insula are associated with the mechanism of eye-head movement coordination. The SEF would send information related to the ongoing SA process to the posterior insula in order to update the new sensorimotor contingency and for the coordination of both movements.

Backward adaptation



Forward adaptation



In addition to also investigate the backward adaptation of RS, Gerardin et al. (2012) investigated the backward adaptation of VS (Figure 19). In this study conducted in our laboratory, they reported modulation of BOLD activation in partially segregated networks for RS and VS adaptation. This study revealed the involvement of common cortical substrates for both adaptation types in the frontal cortex, namely the inferior precentral sulcus of the right hemisphere (and in the left cerebellar hemisphere as well). In addition to that, adaptation of leftward RS led to significant modulations in the right area MT/V5, and in the right Temporo-Parietal Junction (TPJ). In contrast, adaptation of leftward VS yielded significant modulations in the posterior Intraparietal Sulcus and the medial IPS. This involvement of a parietal area in the adaptation of VS is surprising when we consider that the parietal cortex is more involved in generation of RS. However, we already mentioned that the PPC is involved in any kind of sensorimotor transformation.

Furthermore, a TMS study confirmed the involvement of the posterior IPS in VS (Panouillères et al., 2014). In this study, subjects performed both leftward and rightward RS and VS backward adaptation. They applied spTMS to the right posterior IPS (or the vertex as control region) at different times relative to the saccade (0ms, 30 ms, 60 ms, and 90ms). They found that the spTMS-induced perturbation of the posterior IPS at 60 ms after the saccade detection strongly impaired the adaptation of leftward and rightward VS saccades. This impairment was also found in the after-effect of SA. Finally, they reported that the adaptation of rightward RS was facilitated by the spTMS at the 90 ms timing but this effect was not retained in the measurement of the SA after-effect.

Regarding the involvement of the right TPJ highlighted by Gerardin et al. (2012), a recent TMS study disclosed that this area might be involved in the retention of RS adaptation (Péligon et al., 2018). In their study, they applied spTMS over the right TPJ during adaptation of leftward RS (timing after saccade detection: 30, 60, 90, or 120 ms). While they did not highlight an effect of spTMS on the development of SA, they found that the retention of the gain modulation was much larger after spTMS.

Moreover, Guillaume et al. (2018) recently provided evidence of cerebral substrates in SA using fMRI. In their study, they adapted leftward RS in the backward direction. They reported the involvement of the dorsomedial wall of the contralateral precuneus. They also reported that the frontal and parietal areas could encode the error signal following inaccurate saccades. The involvement of the parietal area in this process is further supported by electrophysiological recordings of neurons in monkey PPC (Zhou et al., 2016). They reported two types of response: (1) neurons with persistent pre- and post-saccadic response, and (2) neurons with a late post-saccadic response. They suggested that the former activity encoded the intended end-position whereas the latter encoded the actual end-position of the saccade. Interestingly, the activity of the neurons representing the intended end-position was highly correlated with the discrepancy between intended and actual end-position, and with the probability of corrective saccade occurrence but only after the late response has become available.

The first chapter of the Experimental contributions presents published results supporting the involvement of the human cerebral cortex in SA (Nicolas et al., 2018). **This work was interested in investigating the neurophysiological basis of SA in human using Magnetoencephalography. Moreover, we were also interested in the coupling between SA and visuospatial attention as we will further present in the section Oculomotor space and spatial cognition (section 4).**

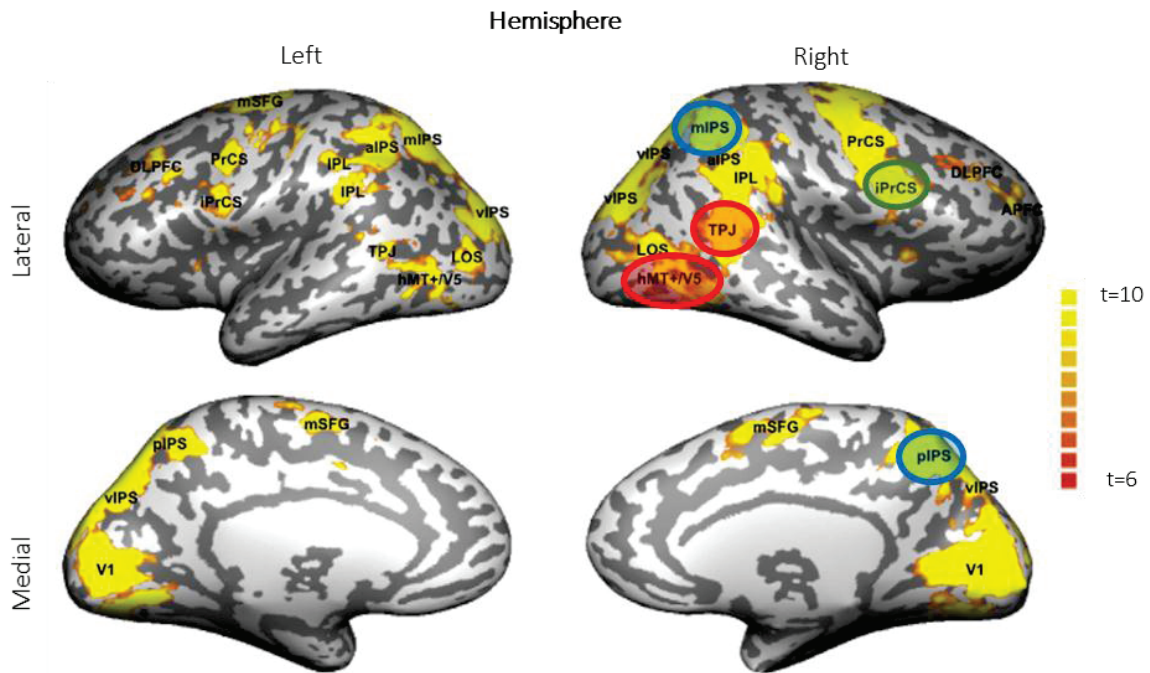


Figure 19: Cortical substrates of saccadic adaptation. Metabolic activation related to saccade generation. The areas represented were significantly activated in the saccades versus fixation contrast. Area circled in red were found to be modulated by the leftward adaptation RS whereas blue shaded areas in the leftward adaptation of VS. The green-circled area was found to be commonly activated in both RS and VS adaptation (adapted from Gerardin et al., 2012).

3. Visuospatial attention

Everyone knows that “Everyone knows what attention is...” (James, 1890). Well, as far as I am concerned, it happened more than once that when someone states ‘*as you all know*’, I don’t. Therefore, this section will be dedicated to try to define what attention is, at least, the type of attention that we investigated in this PhD work.

3.1. An introduction to the attention system

Nature provides a limited amount of resources. Animals are therefore competing for resources and struggling against natural selection. The brain is also limited in terms of resources. External and internal events are competing for neural representation (Ruff, 2013; Bisley, 2011) and struggling for attention selection. In other words, attention is the mechanism that selects fragments among the incredible amount of stimuli brought by our senses to our brain. This selection is meant to prioritize the processing of the selected stimuli to the detriment of the other, non-selected, stimuli. While natural selection is partly based on male finches’ ability to mate, attentional enhancement is based on three main systems: (1) the alerting system, (2) the executive system, (3) and the orienting system (Posner and Petersen, 1990; Petersen and Posner, 2012).

The alerting system can be seen as a cognitive process that produces and maintains optimal vigilance and performance during tasks. Phasic alertness can be described as a transient readiness emerging from a resting baseline. Phasic change in alertness can be induced by a warning signal prior to a target event. Subsequent targets will be detected faster than when no warning signal precedes (Marrocco, 1994). Importantly, the warning signal does not provide information about the upcoming target but changes the speed of orienting attention towards this target (Posner and Petersen, 1990; Petersen and Posner, 2012). Phasic alertness has to be distinguished from tonic alertness, which fluctuates over longer timescales (minutes/hours) and can be indexed to circadian rhythm of wakefulness. This alerting system highly relies on the neuromodulator Norepinephrine (NE). The activation of the locus coeruleus (source of NE) is observed when a warning signal is presented (Aston-Jones and Cohen, 2005). Drugs can, regarding their effect on NE release, either increase or decrease the warning signal effect (Marrocco and Davidson, 1998). Finally, the frontal and parietal cortex are nodes of the NE pathway (Aston-Jones and Cohen, 2005) through which the NE system could influence noradrenergic innervation and therefore cortical control of attention, especially in regions such as the right inferior and superior frontal gyri and the parietal cortex (Marrocco, 1994; Coull et al., 1996; Sara and Bouret, 2012; Masson and Bidet-Caulet, 2018).

The executive system reports to the attentional system when facing complex situations requiring decision making, conflict resolution, task switching, and novelty detection (Bush et al., 2000). This system relies mainly on the frontal cortex with especially the anterior cingulate cortex and the lateral PFC (Stuss, 2011).

The last system of the attentional trinity is the orienting system. This system is specialized in bringing the focus of attention, namely allocating resources, to the selected sensory input. In this focus of attention, stimuli will be prioritized in terms of processing (Eriksen and Hoffman, 1972a; Eriksen and Hoffman, 1972b; Posner, 1980). Attended location or object benefits from enhanced perception that

can result into an improved contrast sensitivity (Carrasco et al., 2000; Cameron et al., 2002) or spatial resolution (Yeshurun and Carrasco, 1999). Attention is amodal, *i.e.* the focus of attention can select stimuli from different modalities such as vision, audition, and touch. The focus of attention can be allocated to a specific feature – featured-based attention – (Treisman and Gormican, 1988), a specific point in time – temporal attention – (Coull and Nobre, 1998), or a specific point in space – spatial attention – (Posner, 1980). **This PhD work will be interested in this latter one in the visual modality, namely visuospatial attention.**

3.2. Meet the orienting system: behavioral experiments

Now it's time to bring my own *original* example to illustrate what spatial attention is. Imagine, I am in the Savanna, hunting for a mammoth steak. I am actively focusing on the part of the landscape where this plentiful probably matriarchal horde is. This focused attention allows me to track their movements and wait for the right time to strike this weak little mammoth baby because it seems to be the simplest individual to kill. Suddenly, my phone rings. For my hunting goal, this event is irrelevant, I should be able to totally inhibit this sensory input because if I get diverted then shift back to the horde, even the frail baby would not be a dinner option anymore. Indeed, they also were alerted by this sudden, relevant for their survival, stimulus and they flew away. To sum up attention allows to maintain goal-directed behavior against distracting events while permitting novel relevant event processing (Chica et al., 2013). This aforementioned daily situation reflects two types of attentional orienting: (1) a voluntary, top-down, **endogenous** one and (2) an automatic, bottom-up, **exogenous** one. Since Posner's seminal study (Posner, 1980), this dissociation has been deeply investigated.

Another important distinction in orienting has to be made. Focus of attention shifts are either accompanied with an eye movement or not. This distinction is referred as **overt versus covert** attentional shift respectively. **The investigation on attentional effects in this PhD work concerned covert shift.**

3.2.1. Paradigms to investigate visuospatial attention

The typical structure of a trial of the spatial orienting paradigm (Posner, 1980) is described in the following (Figure 20). Subjects are presented with a central Fixation Point (FP). In a covert orienting paradigm this FP has to remain foveated during the entire duration of the trial. The FP is flanked by two placeholders, one in each hemifield, at equal eccentricity. Each trial contains two stimuli: the cue and the target. The cue is presented after some delay relative to the start of the trial. Then the target is presented and subjects are instructed to answer only to this latter stimulus (some variants of the paradigm require responding to both stimuli). The delay between the cue and the target is referred to as the Stimulus Onset Asynchrony (SOA). The duration of this SOA is important when considering the dissociation between the two modes of orienting of attention. Usually, short SOA elicit exogenous shifts of attention and long SOA, endogenous shifts of attention. Concerning the cue, its characteristics are also to be considered in relation to the exogenous or endogenous type of orienting of attention elicited. When the cue is peripheral, *e.g.* a change in luminance of one of the two placeholders thus directly providing spatial information, exogenous attention is triggered whereas when the cue is centrally presented and provides spatial information through arbitrate association (*e.g.* 2 different colours or

shapes designating the left vs right spatial locations) endogenous shift of attention is triggered. Concerning the target, it is usually presented in equal proportion between the two sides. Also the target must either be detected or discriminated. In case of detection, a certain proportion of catch trials with no target is inserted, allowing to avoid stereotyped responses to the cue instead of response to the target. The Reaction Time (RT) and/or the accuracy are the dependent variables of this paradigm. After the answer of the subject or after a timeout, the trial ends and an inter-trial interval consisting of an empty display is presented. Regardless of the types of orienting shift elicited, the cues are either valid, invalid or neutral. Valid cues truly inform about the location of the upcoming target, whereas invalid cues provide false information and yield attention shift to a location different from where the target will appear. The neutral cues are uninformative about the location of the upcoming target. The typical pattern observed is that RT to validly-cued targets are faster than RT to neutrally-cued targets which are faster than RT to invalidly-cued targets (opposite pattern for accuracy). The increase in performance, indexed by a decreased RT and/or an increased accuracy, for validly-cued targets as compared to neutrally-cued targets is referred to as the **benefit of attentional orienting**, whereas the decrease in performance between neutrally-cued targets and invalidly-cued targets is referred to as the cost of attentional orienting. The proportion of validly-cued trials can also determine the type of attention shift elicited. In a classical paradigm, 75% of validity is used. In case of 50% validity, a pure exogenous capture is observed (Chica et al., 2014). In case of counter-predictive cues (25% of valid cues), exogenous capture is observed for the validly-cued target while endogenous shift of attention is observed at the opposite location (Chica et al., 2006).

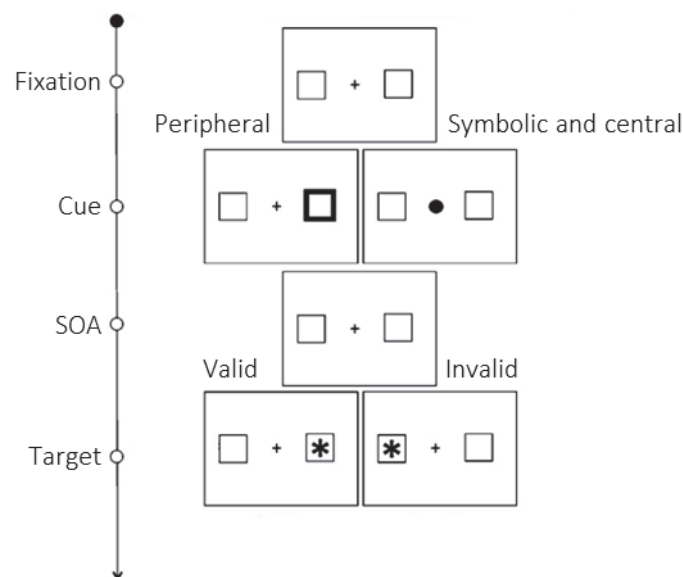


Figure 20: Spatial orienting paradigm introduced by Posner (1980). Subjects are instructed to fixate a central point. After a randomized period, a cue appears. This cue is either peripheral and salient (exogenous orienting) or central, preferably symbolic (endogenous orienting). The Stimulus Onset Asynchrony (SOA) duration also depends on the mode of orienting: short for exogenous orienting (between 50 and 300 ms) and long for endogenous orienting (up to several seconds). Finally, the target appears and the instruction is either a simple detection (necessitating catch trials), or a discrimination regarding a feature of the target, e.g. size, orientation etc. (adapted from Chica et al., 2014).

Endogenous shifts are elicited by spatially predictive cues presented centrally. These cues can be either symbolic or as mainly used, arrows. Note that arrow cues are known to also elicit an exogenous shift of attention preceding the endogenous shift (Hommel et al., 2001; Marotta et al., 2012). It has even been suggested that they elicit a distinct type of attention orienting: automated symbolic orienting (Ristic and Kingstone, 2012). Benefits of endogenous shift of attention are observed for SOA of at least 300 ms long (Remington and Pierce, 1984) and can last for seconds (Posner, 1980). In contrast, benefits of exogenous shifts elicited by peripheral cues are observed for short SOA (50 ms) and are short-lived (Chica et al., 2013). Indeed, after 300 ms, a cost is observed for target presented at the cued location compared to other target locations. This cost, which can last up to 3 seconds (Samuel and Kat, 2003), is related to the Inhibition Of Return (IOR) mechanism (Posner et al., 1985; Klein, 2000). IOR has been proposed to facilitate visual search by avoiding re-inspection of previously explored locations (Klein, 2000).

To sum up, the spatial orienting paradigm has been used intensively to characterize endogenous and exogenous orienting, and has revealed that the latter is faster but that the former is sustained (Müller and Rabbitt, 1989). A subsequent interrogation is whether these two orienting mechanisms are part of a single attentional system or they are two individual attentional systems.

3.2.2. Endogenous and exogenous interactions

In order to accomplish efficient behavior, endogenous and exogenous orienting interact to control the focus of attention. In a single attentional system, the two modes of orienting would be competing for the control of attention (Godijn and Theeuwes, 2002) with the winner controlling where the focus of attention is located. If two attentional systems coexist, performances would be differently modulated by both systems to pursue the individual's goal and react to environmental events (Klein, 2004).

3.2.2.1. Competition for the control of attention

In the framework of a unique attentional system, both orienting modes should share functional characteristics. These characteristics could eventually differ in their quantitative aspects but not qualitatively (Chica et al., 2013). For example, they should share the same coordinates in which attention operates. Moreover, they should share similar neural underpinnings and behavioral representations. To provide evidence for this single attentional system, authors have shown that the exogenous orienting of attention can be modulated by endogenous attention.

Indeed, Müller and Rabbitt (1989) designed a paradigm in which targets were validly or invalidly centrally cued. In some trials, the central cue could be followed by a peripheral cue. The results showed that the exogenous capture of attention was enhanced by endogenous attention when their indication was congruent. When the peripheral cue indicated another location than the central cue, the capture effect was smaller. They interpreted these results as endogenous attention modifying the effect of exogenous attention. In the same vein, Yantis and Jonides (1990) showed that exogenous capture could occur only when central cues were not 100% predictive, meaning that when the attentional load is high (100% valid cues), exogenous cues do not capture attention. Furthermore, studies have shown that the exogenous capture could occur if the cue shares relevant characteristics with the target. In Folk et al.'s (1992) experiments, the cues were either suddenly displayed or represented by a change in color. The to-be-detected target was either a sudden target or a change in color. The results showed that attention

capture occurred only when the cue and the target shared the same characteristics in both conditions. They proposed that exogenous capture was a contingent capture and therefore under the control of endogenous attention. Finally, a set of studies have demonstrated that facilitating effect and IOR can be modulated by the difficulty of the task (*e.g.* detection *versus* discrimination) which is interpreted to be an endogenous modulation of exogenous capture (Chica et al., 2006; Lupiáñez et al., 1997; Lupiáñez and Milliken, 1999). Taken together these results suggest that exogenous orienting is not truly automatic since it can be modulated by endogenous factors, arguing for a single attentional system that can be oriented following two modes.

In contrast with this view, data has provided evidence that exogenous attention is independent of endogenous orienting. Theeuwes et al. (2000) varied the onset time of a distractor and found that it involved costs only when it was presented up to 100 ms before the target. They concluded that exogenous capture always happened but when the cue is not relevant, attention can disengage from the attentional capture and shift back to the task at hand, resulting in no cost at the behavioral level.

3.2.2.2. Independent contribution to performance

Along the differences shown in Table 2, one major argument advanced by the proponents of the two different attentional systems hypothesis is the dissociation between an object-based exogenous attention and a space-based endogenous attention (unless specific instructions requiring endogenous shift to be object based or the focus to be broad) (Goldsmith and Yeari, 2003). One study supporting the idea of such a dichotomy between endogenous and exogenous has used the Illusory Line Motion (ILM) (Hikosaka et al., 1993). This illusion consists in the impression that a line, presented all at once, actually *develops* from one of its extremity. The extremity from which the line develops is the one previously cued. The ILM is produced whenever a peripheral cue is presented near one extremity of the line. When attention is oriented endogenously with central arrow cueing, no ILM is observed. ILM is observed only when endogenous attention is oriented towards placeholders at the extremity of the line. These results suggest that only when endogenous attention is set to be object-based does the ILM occur (Christie and Klein, 2005).

The two orienting modes also modulate processing at different stages. Usually, when a target is presented, the visual evoked response recorded with an Electro- or a Magneto-Encephalogram (EEG/MEG), is composed of the N100 (N for negative), P100 (P for positive), N200 and the P200. These components are modulated by attention orienting (cued *vs* uncued) and they are larger for cued locations (Figure 21).

Hopfinger and West (2006) studied the Event-Related Potentials (ERP) elicited by a target preceded by a central cue which was followed by a peripheral cue. The target could be either valid, or invalid regarding the centrally-cued location, the peripherally-cued location, or both when they were congruent. They showed that the P100 is modulated by exogenous attention while endogenous attention modulates the later processing, namely the P300. Moreover, Chica and Lupiáñez (2009) showed that IOR modulates both early and late processing reflected in the P100 and P300 respectively while endogenous attention produces a stronger modulation of the P300 component (Figure 22 for an example of P300 component).

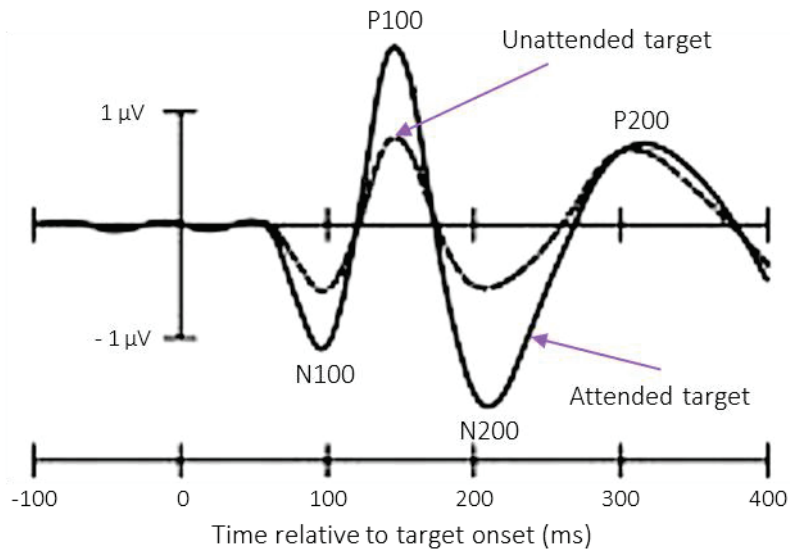


Figure 21: Typical Event-Related Potential elicited by the target in a Posner-like paradigm. The response is observed at electrodes contralateral to the target in visual areas (for a visual target). When the target is presented at the attended location, the N100, P100, N200, and P200 components are larger as compared to target presented at unattended locations (adapted from Hillyard et al., 1998).

Table 2: Dissociation between endogenous and exogenous attention (adapted from Chica et al., 2013)

BEHAVIOUR	ENDOGENOUS	EXOGENOUS
Speed	Slow	Fast
Disruption by memory load	Yes	No
Cue predictability	Yes	No
Spread on objects	Not necessarily	Yes
Disengage deficit after parietal injury	No	Yes
Inhibition of return	No	Yes
Stimulus enhancement	No	Yes
Interaction with non spatial expectancies	Yes	No (IOR: Yes)
Effects on early perceptual processes	Small	Large
Effects on later perceptual processes	Yes	No (IOR: Yes)
Produces illusory line motion	No	Yes
Modulates conscious perception	No	Yes

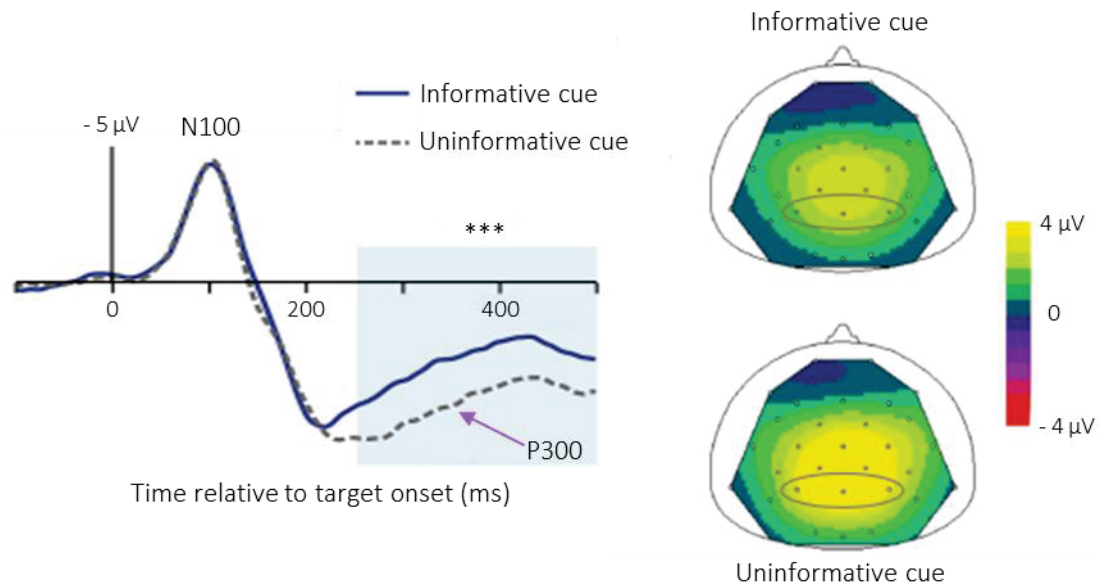


Figure 22: P300 component observed after target onset. **Left Panel:** Time course representing the signal averaged across the outlined (parietal) electrodes on the topographies. This results highlight that the P300 can be modulated by spatial information provided or not by the cue. **Right Panel:** Topographies of the P300 between 250 and 500 ms after onset of the target (blue rectangle in the time course). *** $P < 0.001$ (adapted from Bidet-Caulet et al., 2015).

Endogenous and exogenous attention can also be dissociated regarding their effect on conscious perception. When spatial attention is triggered by exogenous cue, the percentage of reported seen targets increases for valid as compared to invalid trials (increased conscious perception). Conversely, when a symbolic central cue triggering endogenous attention is used, the percentage of seen targets is not modulated by the validity of the cue (Chica et al., 2011b). In the former (exogenous) case, the behavioural results are supported by the electrophysiological marker P100. When targets are preceded by an exogenous valid cue the cue-locked P100 component is larger for seen targets than for unseen targets. This P100 increase indexes the capture of attention that led to better seen targets (Chica et al., 2010).

Finally, it is also known that the link between eye movements and orienting of attention is different for exogenous and endogenous attention (Smith and Schenk, 2012). This dissociation will be presented in more details in the Pre-saccadic shift of attention section (4.4.1).

Thus, this line of research points towards the idea that exogenous and endogenous attention are two functionally distinct attentional mechanisms. To further support this idea, it has to be demonstrated that they are underpinned by segregated, at least partially, neural substrates.

3.3. Stripping the orienting system: neural substrates

To study the neural correlates of attention, a distinction has to be made between the neural correlates of orienting attention and those of the effect of attention on sensory processing. In a Posner-like paradigm, the former would be related to the activity elicited by the cue while the latter relates to the cue-related modulation of activity elicited by the target.

3.3.1. Fronto-parietal networks of the orientation of visuospatial attention

3.3.1.1. Segregation: Dorsal and ventral networks

Among the first studies of the neural substrates of the cue processing, the results reported by Hopfinger et al. (2000) delineated a network including the superior frontal, the inferior parietal and the superior temporal lobes activated during an endogenous orienting task. Kelley et al. (2008) and Yantis et al. (2002) both reported transient activity in the medial prefrontal cortex and the Superior Parietal Lobule (SPL) when attention was disengaged from fixation to a new location. Conversely, during maintenance of attention at peripheral locations the FEF and the IPS were involved (Kelley et al., 2008). This suggests that the SPL would encode changes of spatial coordinates of the focus of attention while the FEF and the IPS would code the ongoing focus of attention location (Molenberghs et al., 2007). The dorsal attentional system is supposed to be bilateral and symmetric. Indeed, it has been reported that the FEF and the SPL activity changes when either side is attended, yet their response is higher for contralateral shift of attention (Perry and Zeki, 2000). Furthermore, recordings in monkey have linked the locus of attention and neural activity in the Lateral Intraparietal (LIP) area (Bisley and Goldberg, 2010).

The causal involvement of these areas in the orienting of attention can also be tested using invasive methods in monkeys or non-invasive techniques in humans. In Monkeys, after chemical inactivation of the FEF (Wardak, 2006), the LIP (Wardak et al., 2004) or after lesion of the PFC (Rossi et al., 2007), a deficit in top-down attention (search tasks ofr Wardak's studies, Posner-like paradigm for Rossi's study) was observed. In humans, Muggleton et al. (2003) inhibited the FEF using TMS and reported that the performance in a conjunction and in a simple feature visual search task in which the target was unpredictable was impaired. Hilgetag et al. (2001) found similar results regarding the parietal cortex. They inhibited both the left and the right parietal cortex using rTMS. They observed that performance of detection for stimuli presented in the contralateral side was impaired. Conversely, performance to ipsilateral targets was increased. They concluded that these data support the theory of interhemispheric inhibition (IHI) first introduced by Kinsbourne in 1977. This theory posits that each hemisphere exerts IHI and the selection of the to-be-attended hemifield results from the winner of this competition.

For target detection, the role of the right TPJ has been reported consistently (Corbetta and Shulman, 2002; Corbetta et al., 2008). In these reviews, the authors claimed that the cue-related activity is not observed in the right TPJ, this latter displaying an increase of both activation and functional coupling with visual areas (Indovina and Macaluso, 2004) only when targets are presented in uncued locations, i.e. when re-orienting is required. Furthermore, the right TPJ response is equal for both target sides (Perry and Zeki, 2000). These studies led some authors to suggest that the right TPJ would be involved in the re-orienting towards unexpected yet relevant targets (Perry and Zeki, 2000; Corbetta and Shulman, 2002; Corbetta et al., 2008). Indeed, the right TPJ has been reported by Corbetta et al. (2000) to be co-activated with the dorsal network when targets are detected, the right TPJ response being enhanced when the target is detected at an uncued location. Other regions are activated by target detection: the Ventral Frontal Cortex (VFC) with the Middle Frontal Gyrus (MFG), the Inferior Frontal Gyrus (IFG), the frontal operculum, and the anterior insula. These regions are activated by relevant targets regardless of their saliency. In contrast, during endogenous tasks, these regions do not activate in response to highly salient distractors (Indovina and Macaluso, 2007). Moreover, Shulman et al. (2003) found that the right TPJ de-activated in response to irrelevant distractors (salient stimuli not relevant for the task at hand). The de-activation was greater when the following target was detected as

compared to a missed target (Shulman et al., 2007). Accordingly, the right TPJ has been proposed as a filter of irrelevant inputs since the more reliable the cue, the greater the deactivation and therefore the filtering out of uncued location.

According to these data, Corbetta et al. (2008) proposed a neuroanatomical model of attention with dorsal and ventral fronto-parietal networks that are functionally and anatomically segregated (Figure 23). According to these authors, the dorsal network is involved in the selection of attended location according to internal goals. This network includes the IPS, the SPL and the FEF. The dorsal network relates to the endogenous control, biasing the processing of stimuli according to endogenous signals. The ventral network detects salient and behaviorally relevant external stimuli, like unattended or infrequent targets. The ventral network includes the TPJ and the VFC, in the right hemisphere. This system is thought to interrupt the dorsal system to change the focus of attention according to the detected stimulus, for which relevance is the main criterion for activation (Downar et al., 2001). The idea of a spatial dorsal network for orienting attention and a ventral network for disrupting it in case of sudden need for re-orienting is further supported by the idea that the FEF and the IPS of the dorsal systems contain external spatial maps and are spatially selective (Beauchamp et al., 2001) while the right TPJ and the VFC are not spatially selective (Macaluso et al., 2002; Macaluso and Patria, 2007).

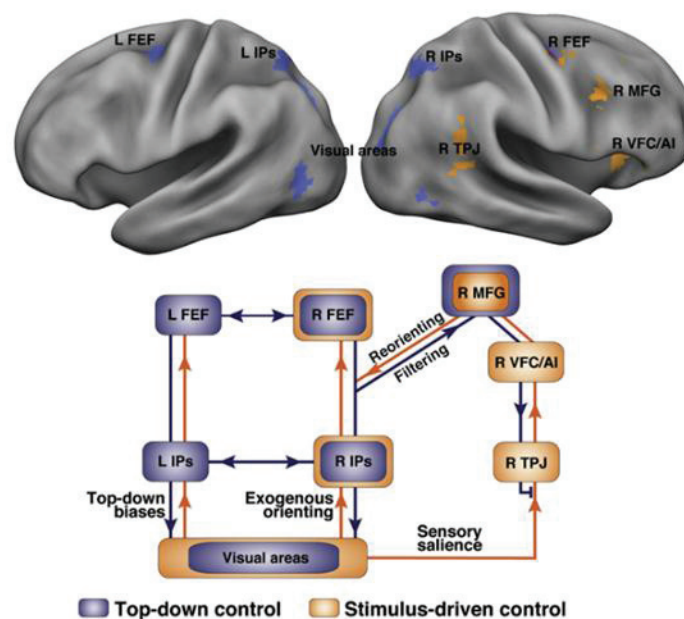


Figure 23: Anatomico-functional model of attention orienting proposed by Corbetta et al. (2008). *Top panel:* Results of a meta-analysis of studies on orienting of attention. Blue represents areas that respond to central cues. Orange represents areas activated when attention is re-oriented towards an unexpected, yet relevant target. **Bottom panel:** Proposed model for the interaction between the ventral and dorsal networks during re-orienting. The dorsal network sends endogenous biases to sensory processing areas and filtering signals to the ventral network (via the MFG). These top-down signals restrict the ventral network to respond only to relevant stimuli and not to irrelevant ones. The ventral network is able to break the dorsal network current activity with a re-orienting signal via MFG.

In addition to this cortical network, strong evidence supports the idea of the involvement of the SC in orienting attention. The activity of SC neurons recorded in behaving monkeys has been linked to the overt shift of attention (McPeck and Keller, 2002) as well as to the covert shift (Ignashchenkova et al.,

2004). The SC has been found to be causally involved in experiments showing that microstimulation of the SC elicits shift of attention (Müller et al., 2005).

For some authors, exogenous orienting of attention that we described in the previous section (see Endogenous and exogenous interactions section, 3.2.2) and the re-orienting system are equivalent. However, the former relates to the attentional capture by salient stimuli unrelated to the task at hand, whereas the latter relates to the processing of relevant stimuli for the task at hand regardless of their saliency. Indeed, among other fMRI studies showing similar results (see for review Corbetta et al., 2008), Kincade's (2005) study supports this distinction between two different mechanisms, exogenous orienting and re-orienting. In this study, this author compared fMRI BOLD activation during the cue and the target periods. In their design, the cues could be either endogenous, exogenous or neutral. The endogenous shift led to an activation of the FEF and the IPS. Exogenous shifts recruited occipital regions as well as the FEF and the IPS (the two latter were less activated as compared to endogenous shifts). Interestingly, the right TPJ and the right IFG activated for exogenously invalidly-cued trials. This study confirms that the dorsal network is more involved in endogenous shifts than exogenous one. Moreover, it indicates that exogenous orienting could be also underpinned by the dorsal network. However, one concern should be raised regarding the fMRI: is it an adequate tool to investigate the exogenous orienting of attention? Indeed, the fMRI time resolution of several seconds does not allow to study a fast process as the exogenous orienting of attention observed in the 300 ms after the cue (Chica et al., 2014; Chica et al., 2013). Noteworthy, the study aforementioned, claiming the use of exogenous cues, used a 2 sec SOA and the behavioral results do not reveal a benefit from these cues.

Yet, in the previous section (Endogenous and exogenous interactions, 3.2.2) we presented evidence for distinctive attentional systems for endogenous and exogenous orienting. It seems therefore likely that these two systems are at least partially segregated as suggested by Corbetta et al. (2008). Moreover, as we will detail in the section 3.4 (Dysfunction of the orienting system: neglect, a pathological model for spatial attention), neuropsychological data support the idea of the involvement of the ventral fronto-parietal network in exogenous orienting. Indeed, patients with neglect following lesion to these regions show an impairment of exogenous orienting and not of endogenous orienting (Bartolomeo and Chokron, 2002). Moreover, TMS studies have provided evidence for the involvement of right TPJ in exogenous orienting. Chica et al. (2011a) used TMS to stimulate the right TPJ or rIPS. They showed that the stimulation of both of these areas produced a greater cue benefit and a longer SOA period to produce IOR.

Finally, endogenous and exogenous systems can be differentiated by the neural activity that underlies them. Indeed, Buschman and Miller (2007) showed in monkey that during endogenous orienting, the PFC neurons activity precedes the PPC activity, whereas during exogenous orienting, the PPC neurons activity precedes the activity of those in the PFC. Moreover, the synchrony between these two areas was found in different oscillatory rhythms. Beta band synchrony increased during endogenous orienting while gamma band synchrony increased during exogenous orienting.

While the functional segregation of these two systems is still under debate, their anatomy is well characterized. To further support this, it has been shown that these two networks are also segregated at rest. Fox et al. (2006) reported that the spontaneous BOLD activity observed with fMRI distinguished a bilateral dorsal attentional and a right-lateralized ventral network, with the activity of both networks correlating with the activity of prefrontal regions.

3.3.1.2. Dialogue is always part of the solution

To behave in coherent way, the two attentional systems have to interact. These interactions are supported by anatomical structures and electrophysiological mechanisms.

Anatomical substrates of communication

Asplund et al. (2010) proposed the right Inferior Frontal Junction (IFJ) to be the hot spot of the dialogue. The IFJ is co-activated with dorsal network areas during the cue period in a goal-directed task: its activity is positively correlated with FEF and IPS while negatively correlated with the right TPJ. In contrast, in case of re-orienting, the pattern was reversed: right TPJ-IFJ correlation was positive and IPS-IFJ correlation was negative.

The right MFG could also be a spot of communication between the two networks. Fox et al.'s (2006) resting state study, indeed, revealed that this area could link the two networks since its spontaneous activity is correlated with both dorsal (FEF and IPS) and ventral (TPJ) fronto-parietal networks. Finally, frontal cortical areas as the anterior cingulate cortex, the medial superior frontal cortex and the bilateral anterior insula and frontal operculum are also putatively involved in linking the two networks since they showed cue onset-related and sustained activities in different kinds of attention tasks involving both types of attention allocation (Dosenbach et al., 2006).

A set of studies in human and non-human primates have brought the Superior Longitudinal Fasciculus (SLF) connecting parietal to frontal areas as a good candidate for communication both within and between the dorsal and ventral attention systems (Figure 24). In an influential paper, Thiebaut de Schotten et al. (2011) studied, on the one hand, the anatomy of subjects' three branches of the SLF and on the other hand, subjects' visuospatial attentional bias with a line bisection task. First, they found that the SLF I was symmetrical, the SLF II tend to be lateralized in the right hemisphere and the SLF III was strongly lateralized in the right hemisphere. Moreover, they showed that the degree of right lateralization of the SLF II correlated with leftward biases in the line bisection task. These results suit well the fact that the SLF I overlap with the dorsal attentional network activated during orienting of spatial attention, the SLF II overlaps with the parietal component of the ventral network and the prefrontal component of the dorsal network and the SLF III overlaps with the ventral fronto-parietal network.

Electrophysiological mechanisms of communication

Oscillatory activity can be observed at the individual neuron level as repeating spiking patterns. When this spiking pattern co-occurs in different neurons, they have oscillatory synchronous activity. In human recording at the single unit level is rare. Yet, it is possible to record local field potentials in epileptic patients through either intracranial electrodes or subdural electrodes which have been implanted for the purpose of pre-surgical evaluation. Fortunately, oscillatory activity can be measured in healthy subjects using EEG and MEG.

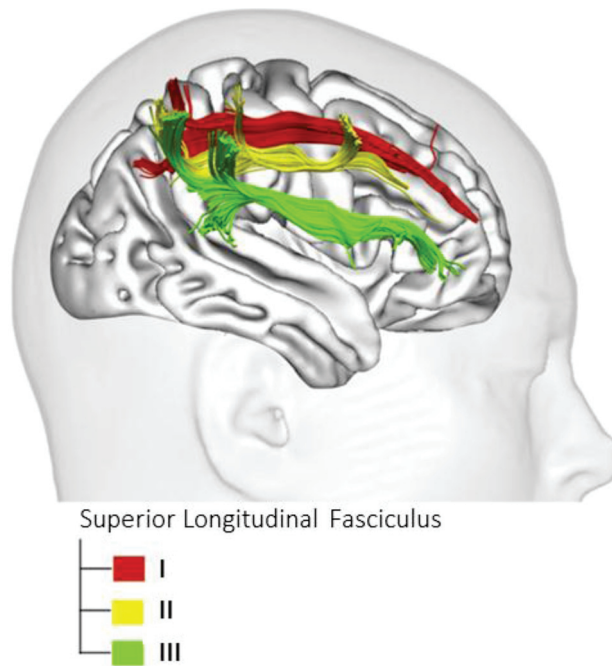


Figure 24: *The three branches of the superior longitudinal fasciculus described by Thiebaut de Schotten et al. (2011). The Superior Longitudinal Fasciculus (SLF) I overlaps with the dorsal network of attention and is symmetrical, the SLF III overlaps with the ventral network of attention and is right lateralized. The SLF II tends to be lateralized to the right and overlaps with the parietal component of the ventral network and the prefrontal component of the dorsal network. These SLF could be the anatomical support of communication between the different areas involved in orienting attention (adapted from Chica et al., 2013).*

The recorded activity represents the sum of activity of large neuron assemblies. Oscillatory activity is defined by three main variables (Figure 25): (1) the frequency, namely the speed of the oscillation (number of cycles per second); (2) the power, namely the amount of energy in a frequency band (when the number of neurons oscillating in synchrony increases, the power in the frequency band increases); and (3) the phase, namely the position along the sine wave at any given time point. The oscillatory activity is usually represented by time-frequency representation of power. Usually, the oscillations are loosely clustered in five typical frequency bands delta (1-4 Hz), theta (4-8 Hz), alpha (8-14 Hz), beta (15-35 Hz), and gamma (>35 Hz). In this section, we will focus on alpha and gamma oscillations since they are the most investigated in the attention framework.

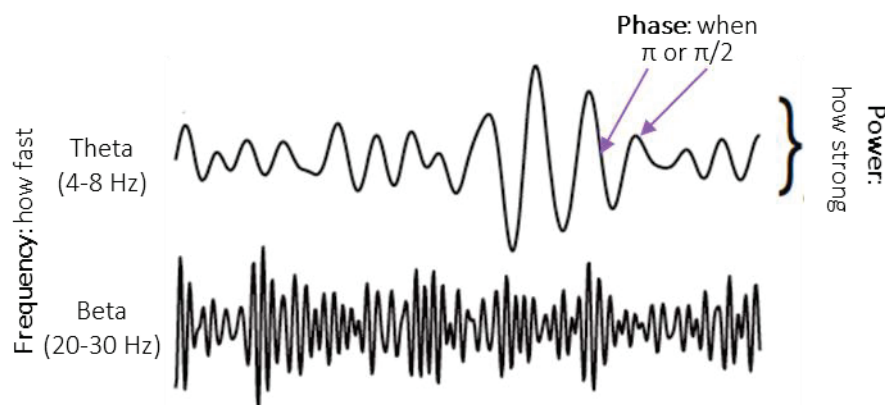


Figure 25: *Definition of oscillatory activity. Three parameters define oscillations: The frequency, the power and the phase (adapted from Cohen, 2014).*

Alpha oscillations are more prominent when awake people close their eyes and has therefore been proposed as a marker of cortical idling (Pfurtscheller et al., 1996). However, new hypotheses have brought up a more active role of alpha oscillations. Among them, the gating by inhibition hypothesis of Jensen and Mazaheri (2010). The probability of neurons to fire depends on the amplitude of the alpha oscillations. Alpha oscillations reflect alternation of high excitability -release of inhibition- periods during which alpha power decreases (alpha desynchronization), and low excitability phases during which alpha power increases (alpha synchronization). In a given task, neural pathways are either task-relevant or task-irrelevant. According to the gating by inhibition hypothesis, alpha power should increase in task-irrelevant pathways, while decreasing in task-relevant pathways. In support of this hypothesis, studies have consistently showed that the cue-related activity (from the cue onset to the target onset) is reflected in the alpha band which synchronizes in the visual areas ipsilateral to the attended hemifield while desynchronizing in the contralateral visual areas (Thut, 2006; Marshall et al., 2015; Rihs et al., 2007; Rihs et al., 2009; Worden et al., 2000; Kelly et al., 2006). Moreover, the alpha power has also been found to correlate with behavioral performance (Thut, 2006; Bonnefond and Jensen, 2012), the more alpha power decreased (desynchronized) in the relevant regions, the faster participants were. Alpha oscillations have also been found to be causally involved in perceptual performance in areas higher than primary sensory areas in the attentional network. Romei et al. (2010) used TMS to entrain alpha band frequency oscillations on the parietal or the occipital lobe. They showed that for both stimulated areas, visual detection of target in one hemifield was impaired when alpha was entrained in the contralateral hemisphere while it was enhanced when the ipsilateral hemisphere was stimulated. Furthermore, Capotosto et al. (2009) applied TMS to the IPS and the FEF during a Posner-like experiment. First performance was impaired and second, this decrease in performance was accompanied by a disruption of alpha desynchronization in the task-relevant visual areas. Moreover, this disruption correlated with the behavioral performance. Consequently, these authors suggested that the fronto-parietal network controls attention through modulation of alpha oscillations. The coordination between the different areas of the attentional system would be underpinned by synchrony in alpha oscillations. Yet, power is not the only component of alpha oscillations that has been uncovered as playing a role in perception. Indeed, the phase of the oscillation has also been linked to perceptual performance. Busch et al. (2009) reported that the probability of a hit increases if the stimulus was displayed simultaneously with a certain phase of alpha oscillations.

Gamma oscillations refers to fast cortical oscillatory activity with frequency above 35 Hz (firing pattern every 10-30 ms). Along with the alpha oscillations, the gamma rhythm has been considered as playing an important role in perception. Especially, it has been proposed as playing a prominent role in perceptual binding which refers to the phenomenon of grouping elementary features of stimuli which is required to perceive them as a coherent whole. This idea is supported by results in monkey (*e.g.* Aston-Jones and Cohen, 2005) and in human (*e.g.* Tallon-Baudry and Bertrand, 1999). The binding mechanism would be underpinned by synchronizing assemblies of neurons processing distinct features. Two main types of Gamma Band Activity (GBA) have been distinguished in the literature: (1) evoked and (2) induced. The evoked GBA appears with the same latency and phase after each stimulus onset and is usually of lower frequency. The induced GBA is not temporally tightly linked to the stimulus and is reflected in higher frequencies. The gamma oscillations can also be divided according of the broadness of their range: narrowband (approximately +/- 5 Hz centered at 60 Hz) or broadband gamma being preferentially involved in perception (Fries et al., 2001; Lachaux et al., 2006; Sedley and Cunningham, 2013). Gamma oscillations have also been linked to attention, yet following a reversed pattern to the

one of alpha oscillations. Indeed, an attended stimulus will be preceded by an increase of gamma power in sensory areas (Fries et al., 2001; Fries et al., 2008; Womelsdorf et al., 2006; Popov et al., 2017; for review see Fries, 2009). But GBA modulation is not only observed in sensory cortices and consequently, GBA would more generally reflect activation of task-relevant processes across the entire brain. For example, Akimoto et al. (2014) found gamma modulations in the MFG for target *versus* non target in a visual oddball paradigm. Moreover, the synchrony between the right and the left MFG and between the right MFG and the thalamus correlated with individual processing speed. The power of gamma in the left MFG was correlated with accuracy and the power in the left thalamus and the left IPS with the processing speed. Therefore, GBA correlates with performances, the stronger, the better. Fries (2005) suggested that GBA would subtend communication between brain regions. In the attention system, evidence has been provided in human by Baldauf and Desimone (2014). They reported MEG results showing that the gamma synchrony increases between the IFJ and the fusiform face area when subjects attend to faces and with the parahippocampal place area when participants attend to places.

These sets of studies brought the idea that alpha oscillations are involved in feedback signaling, while gamma oscillations are involved in feedforward signaling as it has since been conceptualized by several model including the ‘Communication between Brain Areas Based on Nested Oscillations’ model by Bonnefond et al. (2017) presented below. Initially supported by data from the rat visual system (von Stein et al., 2000), the idea of gamma oscillations supporting bottom-up interactions and lower frequencies including alpha supporting top-down interactions was also supported by data in monkeys (Buschman and Miller, 2007) and human (Michalareas et al., 2016). Buschman and Miller (2007) found that the coupling between prefrontal and parietal areas was directional. Namely, when attention was captured, coupling in the gamma band was found to be led by the parietal cortex while the pattern was reversed when attention was endogenously oriented.

Regarding the influence of both alpha and gamma oscillations in the attentional network, one can suggest that the interaction between exogenous and endogenous attention is subtended by a cross-frequency coupling between high frequency oscillations indexing the activity of the ventral, exogenous, system of attention and low frequency oscillations coordinating the dorsal, endogenous system of attention. Among others, Bonnefond and Jensen (2015) showed that the power of gamma oscillations was coupled with the phase of alpha oscillations. Moreover, this coupling correlated with performances. Also, Chacko et al. (2018) reported that, when participants performed a Posner-like paradigm, RT negatively correlated with the strength of the coupling between amplitude of alpha and gamma oscillations, the higher the coupling, the faster the subject’s response.

In order to wrap-up these body of literature, Bonnefond et al. (2017) proposed that ‘Communication between Brain Areas Based on Nested Oscillations’ (Figure 26). This model still needs further evidence in the attentional framework. However, it is a usefull framework to deepen our understanding on brain communication based on oscillatory activity. Here it goes:

- (1) Long distance communication is underpinned by inter-areal phase synchrony in the alpha band (A to C or A to B communication in Figure 26). Neurons in A and in C communicate if they oscillate coherently and if the alpha power is decreased. In B, neurons have high alpha power and asynchrony with C neurons, the communication is therefore blocked.
- (2) Gamma oscillations are nested within alpha oscillations. Since in A, alpha power is low, burst of gamma band oscillations are more likely to occur and last longer. Moreover, in C, low alpha

also allows gamma oscillations to occur. The synchrony of alpha frequency leads to a synchrony in gamma oscillations between A and C.

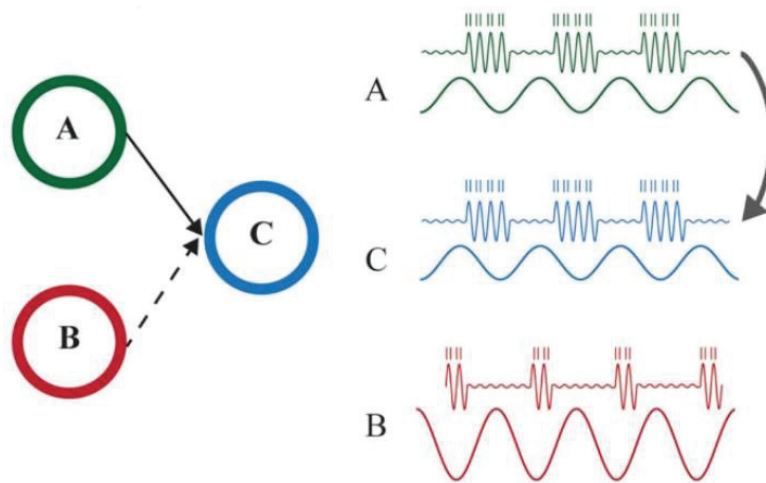


Figure 26: Communication between brain areas based on nested oscillations (Bonnenfond et al., 2017). Alpha power guides the functional connection between nodes of the attentional network. Gamma band activity travels from A to C. The communication between B and C is blocked because of high power in the alpha band at the B node and because of an asynchrony between B and C. Both the alpha power modulation and the synchrony between nodes and frequency bands contributes to the routing of information.

Gamma oscillations are of particular interest in this PhD work. GBA seems to play an important role in communication within brain networks in general, and more specifically in selecting relevant information during attention orienting. Moreover, GBA has been shown to be enhanced after visuo-manual learning, in sensors above the right parietal lobe (Perfetti et al., 2011) and Soto and Jerbi (2012) showed that the coupling between low frequency delta band and high frequency gamma band was increased after visuo-motor adaptation. **We hypothesized that GBA could be the signature of oculomotor plasticity and the neurophysiological basis of the coupling between attention and SA.**

3.3.2. All this for what? Consequences of attention on neural processing

Now, we have an idea of where and how attention directs its focus. Yet, we still need to shed light on what this focus of attention creates at the neuronal level.

The endogenous modulation of sensory signals strengthens the neural representation of attended stimuli relative to noise in the neural activity (Reynolds and Heeger, 2009) which is observed as an increase in firing rate, a change in ERP, in oscillatory activity, or increase in BOLD signal (see for review Ruff, 2013). These changes are observed in the regions specialized in the processing of the attended stimulus feature. Moreover, reduced neural processing is observed for distractors (Hopf, 2006; Seidl et al., 2012; Lavie, 2005; Bidet-Caulet et al., 2007; Bidet-Caulet et al., 2010).

Recordings in behaving monkeys have allowed to highlight that neurons respond more to stimuli falling in their receptive field when this location is attended. These results have been shown in most visual areas, from the LGN to the middle temporal area (see Bisley, 2011 for review).

The neuron firing rates also increase with the stimulus contrast. Therefore, two hypotheses about the effect of attending to a stimulus have been proposed: either (1) the contrast-response curve shifts in a way that less contrast is required for eliciting a given firing rate, or (2) the gain of the neural response increases such as firing rate increases for the same contrast. Reynolds and Heeger (2009) found that when the stimulus was smaller than the attended area, a shift was observed, whereas when it was bigger, a gain was observed. They consequently proposed the normalization model of attention, trying to explain the effect of attention at the neural population level. This model comprises three main components: (1) the stimulation field, (2) the suppressive field, and (3) the attention field. The interaction between these three components results in the population response (Figure 27).

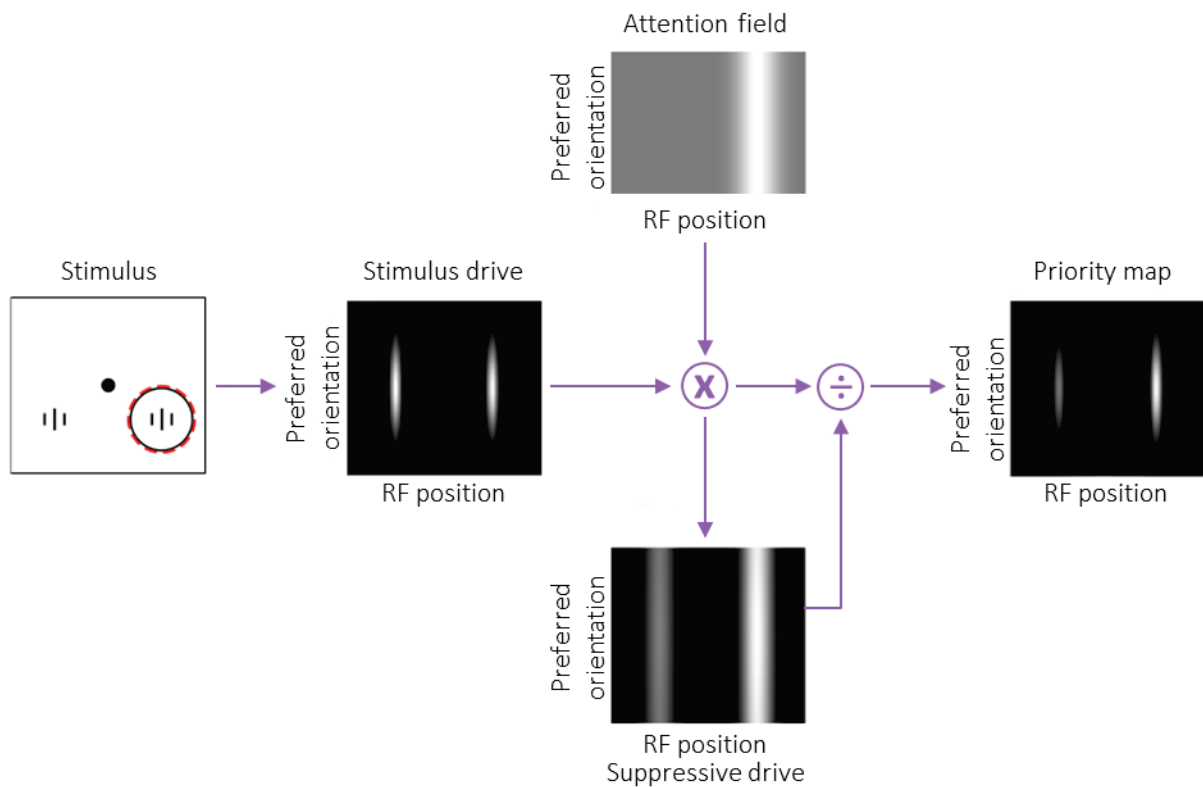


Figure 27: The normalization model of attention (Reynolds and Heeger, 2009). The population response results from the stimulus drive multiplied by the attentional field and then normalized by the suppressive drive. The fixation point is represented by the central dot on the left panel. The solid circle represents the Receptive Field (RF) of a neuron selective for the orientation of the grating presented inside the RF. The dashed red circles represent the attentional focus. The stimulus drive represents the response of neurons without attentional field nor suppressive drive as a function of their orientation preference and their RF spatial position. The attentional field represents the gain of attention when attending to the right side of the experimental display. The suppressive drive is computed by multiplying the stimulus drive by the attentional field. The population response results from the normalization by the suppressive drive of the stimulus drive multiplied by attention field.

State of the art

- The stimulation field, or stimulus drive, is defined as the range of spatial positions and orientations (as an example of stimulus feature) in which the stimulus evokes an excitatory response. Each neuron represented in the stimulation field is characterized by its RF center (x-axis in Figure 27) and preferred orientation (y-axis in Figure 27).
- The suppressive field, or suppressive drive, comes from a set of neurons defined by their spatial positions and preferred orientations leading to a response suppression. Neurons with close RF but different preferred orientation exert reciprocal inhibition.
- The attention field relates to the value of the gain across spatial positions and orientations. It is assumed to be 1 everywhere except for the attended position for which the value increases.

In the model, the effect of attention results in the multiplication of the stimulus drive and the attentional field. The result of this computation is normalized by the suppressive field. This computation results in the population response (priority map in Figure 27).

Finally, Bisley (2011) proposed that the selection of location depends on priority maps. This hypothesis posits that fronto-parietal networks use maps of the visual world in which items (e.g. locations) are represented by activity proportional to their attentional priority. The priority results from a combination of exogenous inputs and endogenous factors. The overt or covert shifts of attention are directed towards the peak of the priority map (Figure 28).

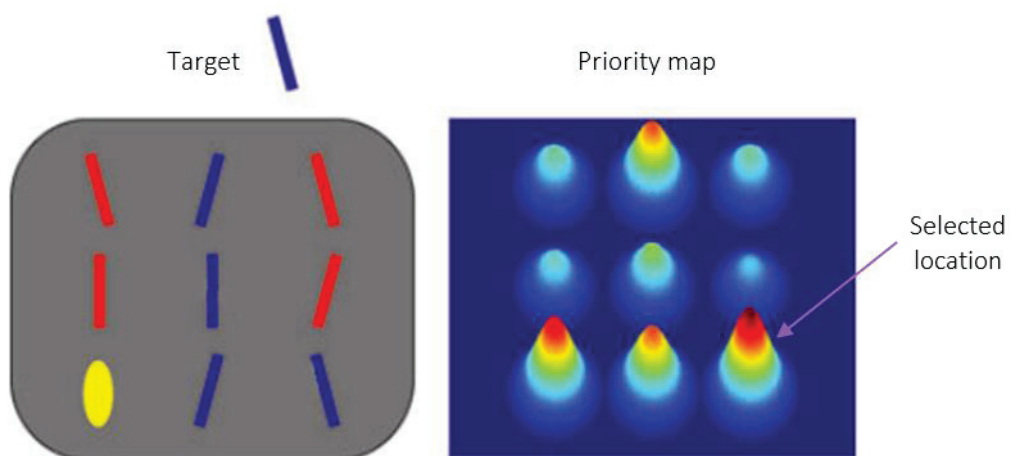


Figure 28: Priority map hypothesis (Bisley, 2011). **Left panel:** visual search task. **Right panel:** neuronal activities on a priority map. Red stimuli in a different orientation present poor activity. Blue stimuli elicit more activity. Bars with the same orientation also elicit more activity. The salient yellow stimulus elicits high activity. The strongest activity is elicited for the target.

3.4. Dysfunction of the orienting system: neglect, a pathological model for spatial attention

3.4.1. Definition

Neglect is a consequence of brain damage, usually strokes, in different cortical and subcortical areas. In a chronic phase, only right brain damages cause persistence of this syndrome. Consequently, Neglect Patients (NP) refers to right brain damage patients with left hemi-space and/or hemi-body spatial deficits, namely difficulties to detect and respond to stimuli in the contralesional space. Yet, the set and the severity of symptoms involved in spatial neglect vary between patients, there are four key symptoms defining this condition. These symptoms are: (1) a reduction of arousal (or alertness as defined in the previous section - An introduction to the attention system, 3.1) and speed of processing; (2) a failure to attend and report stimuli in the contralesional side, in absence of perceptual visual deficits; (3) a rightward (ipsilesional) attentional bias; (4) awareness disorders including anosognosia and confabulation about body ownership (Bartolomeo and Chokron, 2002; Corbetta and Shulman, 2011).

According to Corbetta and Shulman (2011), the core of spatial neglect is the deficit of spatial attention mapped into an egocentric frame of reference. NP experience a continuous gradient of spatial deficits. The performance to behaviorally relevant stimuli improves from left to right (Pouget and Driver, 2000). Moreover, the spatial bias of NP is evidenced in search tasks and eye scanning patterns or even at rest. The gaze of these patients is strongly deviated towards the right hemi-space (Figure 29) (Fruhmann Berger et al., 2008). This spatial bias also exists in the dark (Hornak, 1992). The bias is, in the majority of NP, egocentric, namely in relation to the body midline. However, it also happens that the bias is allocentric, *i.e.* centered on the stimulus (Marsh and Hillis, 2008).

Saying that NP have deficits for orienting their attention towards the left hemifield seems a little simplistic since in the last 20 pages or so, we have discussed a clear distinction between two attentional orienting systems. Moreover, the spatial deficits of orienting attention can result from three different mechanisms: (1) a rightward attentional bias (Kinsbourne, 1977); (2) a deficit in disengaging attention from right-sided events to left-sided events (Posner et al., 1984); (3) a deficit in orienting attention to the left contralesional side (Heilman and Valenstein, 1979).

The rightward bias has been first encompassed in the opponent processor model which relies on interhemispheric inhibition. This model relies on two assumptions: (1) each hemisphere is in charge of orienting attention towards the contralateral hemi-space and (2) in the neurotypical population, there is a tendency to orient towards the right. Right brain damages would exacerbate this rightward tendency by releasing right hemisphere inhibition onto its left counterpart. However, this model can be refuted by several pieces of evidence. First in the line bisection task, a small leftward bias is observed in the neurotypical population, known as 'pseudo-neglect effect' (Bowers and Heilman, 1980). Second, as presented in the preceding section (Stripping the orienting system: neural substrates, 3.3), the attentional system is right lateralized especially when it comes to exogenous attention. However, this idea of IHI can still be encompassed in a right hemispheric dominance for attention framework. Indeed, the damaged right dominant hemisphere, would release its inhibition on the left hemisphere which would result in a rightward bias in attentional orienting. As stated earlier, NP have a tendency to direct their gaze towards the right hemifield. Moreover, De Renzi et al. (1989) showed that NP orient their

gaze towards the rightmost stimulus of a visual scene. Finally, Gainotti et al. (1991) showed that NP start their visual exploration on the right side of space when neurotypical subjects start on the left side. However, this hypothesis of a left hemisphere freed from right hemisphere inhibition is not entirely supported by functional imaging. Indeed, a hypometabolism is observed in both the left intact and the right damaged hemispheres (Fiorelli et al., 1991) and recovery is indexed by restoration of a normal metabolism in the intact left hemisphere (Perani et al., 1993). Finally, Bartolomeo et al. (2001) among others reported that NP were slower than neurotypical subjects when responding to right ipsilesional stimuli.

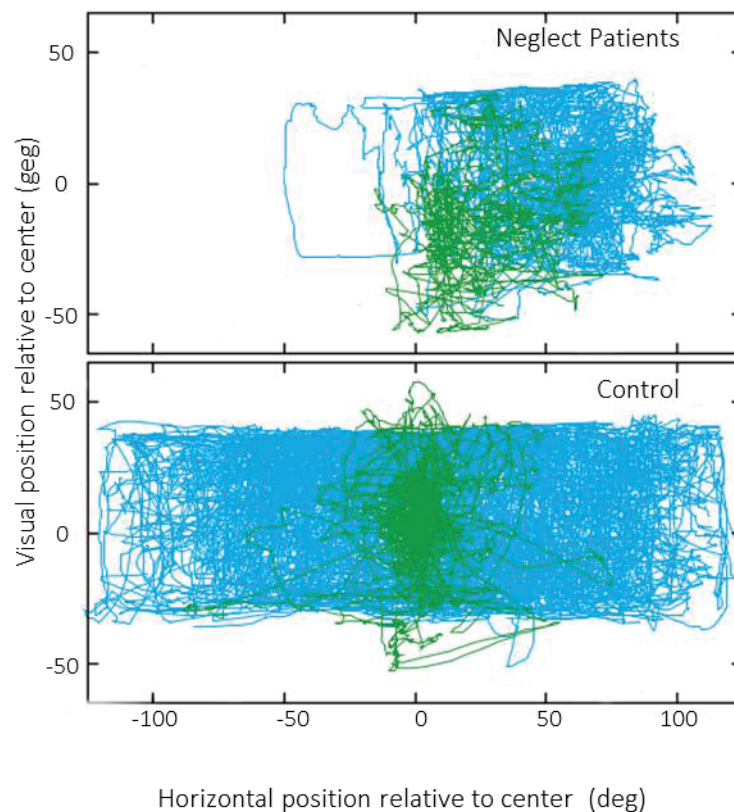


Figure 29: Rightward bias of neglect patients' gaze. Blue traces represent scan path in a visual search while green traces represent scan path at rest for patients (**top**) and control (**bottom**) subjects (adapted from Fruhmann Berger et al., 2008).

The deficit of disengaging attention from the right side of space has been first proposed by Posner et al. (1984). To further support this idea, Morrow and Ratcliff (1988) had NP performing an exogenous Posner-like paradigm. The patients exhibited a greater cost for targets on the contralesional side (invalidly cued on the right side). The cost positively correlated with the severity of neglect symptoms. A meta-analysis of Losier and Klein (2001) reported that the disengagement deficit is robust following peripheral, but not central, cues and that it is stronger for short SOA than for longer SOA. These results suggest that NP patients have attentional deficits restricted to the exogenous system of attentional orienting. Further supporting this idea, Duncan et al. (1999) designed a task in which patients were briefly presented with one vertical string of letters either on their left or right side. They either had to report all the letters or only the one with a specific color. In the former case, NP were impaired equally

for both sides probably resulting from an overall impaired and slower processing capacity. In the latter case, NP's performances were comparable to neurotypical subjects. The authors concluded that NP had a preservation of endogenous control of attention. These studies fit well with Gainotti et al.'s (1991) claim that neglect results from an initial automatic shift towards right events (D'Erme et al., 1992) and a deficit in re-orienting towards left events.

To sum up, attentional deficits of (most) NP are represented in an egocentric frame. These deficits follow a gradient from left to right. Because neglect symptoms can be modulated by several factors such as verbal cues (Riddoch and Humphreys, 1983) or level of alertness (Baldauf and Desimone, 2014), it is likely that neglect syndrome is influenced by other cognitive processes than only a deficit in exogenous orienting of attention. Finally, the attentional deficit might emerge from a deficit in disengaging attention from right to left hemi-spaces.

3.4.2. Neural basis

3.4.2.1. Spatial deficits

The neural basis of neglect is a tricky question. Indeed, lesion in various cortical and subcortical regions can result in neglect syndrome (Figure 30). Initially, neglect was associated with the inferior parietal lobule (Vallar and Perani, 1987). But subsequent studies have highlighted other regions: superior temporal gyrus (Karnath et al., 2001); IFG (Husain and Kennard, 1996); MFG (Corbetta and Shulman, 2011). Also, the most severely impaired patients have damage in the white matter especially at the level of the SLF II and III and the arcuate fasciculus (Thiebaut de Schotten et al., 2005; Bartolomeo et al., 2007; He et al., 2007). On top of that, neglect is sometimes associated with subcortical damage of deep nuclei such as the pulvinar, the caudate or the putamen which likely causes remote hypoactivation of the aforementioned cortical regions (Karnath et al., 2005). When considering all neglect symptoms, attempting to identify critical region(s) failed. Moreover, some regions known to cause neglect are not involved in encoding the normal behavior of the observed deficits. For example, the spatial deficit observed in neglect should result from impaired space representation. Yet, the spatial maps used in orienting attention are thought to be subtended by the dorsal network of attentional orienting whereas the ventral network activates for any relevant stimulus regardless of its spatial position in external space (Corbetta et al., 2008). Accordingly, Corbetta and Shulman (2011) proposed that neglect results from physiological abnormalities emerging from one node of a network specialized in spatial processing and impacting the entire network including the interactions between the fronto-parietal dorsal and the ventral network.

Aside the ventro-dorsal interactions, the interhemispheric inhibition might play a role. When considering hemispheric responses towards a contralateral stimulus, studies have consistently shown that the most reliable spatial coding metrics is the ratio of evoked activities between left and right hemispheres rather than the raw evoked activity of either hemisphere, either in fMRI (Sylvester et al., 2007) or in electrophysiological studies in humans (Thut, 2006) and in monkeys (Bisley and Goldberg, 2003). Therefore, it has been postulated that the attentional focus location could be encoded by both hemispheres through a difference signal emerging from their interactions (Innocenti, 2009). This remote effect of the ventral network on the dorsal one has been evidenced by two main studies. First, Corbetta

et al. (2005) showed that in the acute phase, the dorsal network exhibited an hypoactivation in the left and right hemispheres during a spatial attentional task and that it was accompanied by an interhemispheric imbalance activity in dorsal parietal cortex. Interestingly in the chronic phase, symptoms ameliorated and this imbalance decreased. Second, He et al. (2007) showed that NP in the acute phase have a decreased coherence between left and right parietal regions which improved with neglect symptoms improvement. Accordingly, neglect behavior could be interpreted in the framework of the interhemispheric imbalance theory as detailed in the next section (Rehabilitation, 3.4.3).

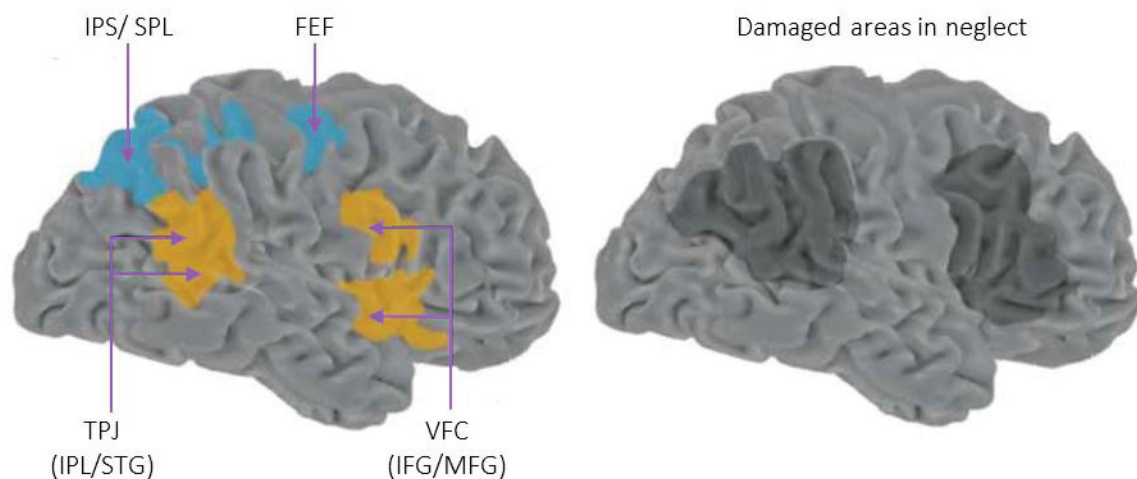


Figure 30: Comparison between the fronto-parietal network of attentional orienting and the network where lesions result in neglect. The ventral fronto-parietal network is impaired in neglect syndrome while the dorsal network is spared (adapted Corbetta and Shulman, 2002).

3.4.2.2. Non spatial deficits

As already mentioned in a previous section (Segregation: Dorsal and ventral networks, 3.3.1.1), the ventral fronto-parietal network would be involved in the re-orienting of attention in response to behaviorally relevant stimuli regardless of their position in the visual field. Following up, Rengachary et al. (2011) replicated these results in NP and showed that this disengagement deficit was even larger and was observed for both hemifields when the VFC was damaged. According to Corbetta and Shulman (2011), this re-orienting deficit is also accompanied by an arousal deficit which would be right lateralized (Figure 31). Indeed, the locus coeruleus/NE system in rats shows a right dominance (Robinson, 1985 in Corbetta and Shulman, 2011). A right hemisphere dominance for arousal control is supported by lesion studies showing that right frontal damage decreases arousal and sustained attention (vigilance) performances. Moreover, arousal was tested with auditory stimuli in two groups of right lesioned patients, with or without neglect symptoms. The performances to the task assessing arousal could discriminate between the two groups of patients (Robertson et al., 1997).

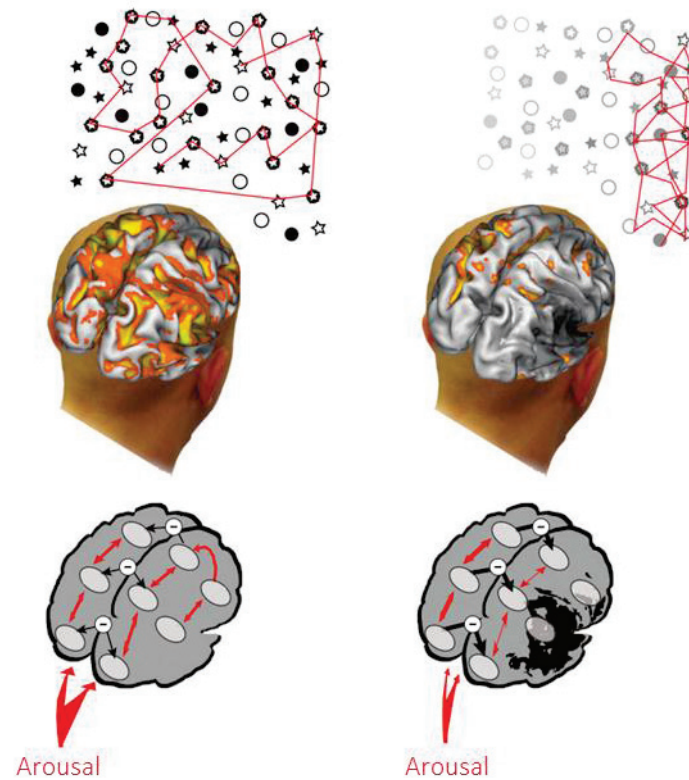


Figure 31: Pathophysiology of spatial neglect according to Corbetta and Shulman (2011). The ventral network is right lateralized, and receives inputs from the locus coeruleus/norepinephrine arousal system which is also lateralized. **Left Panel:** In neurotypical subjects, neural activity related to visual search is symmetrical (**top panel**), interhemispheric inhibition is balanced between left and right. **Right panel:** in NP, damage in the ventral network reduces arousal, target detection and re-orienting in the left hemifield and drives attraction towards the right hemifield.

3.4.3. Rehabilitation

In the rehabilitation of neglect, two strategies can be distinguished: (1) a top-down, endogenous approach which requires an active participation of the patients and in which patients are endogenously cued (by verbal cues for instance) to attend to the neglected visual field; (2) a bottom-up, exogenous, approach which manipulates sensorimotor contingencies. The most commonly used bottom-up approach is the Prismatic Adaptation (PA). This is not odd. Indeed, since Rossetti et al.'s (1998) seminal study showing a benefit of PA on neglect behavior (Figure 32), this rehabilitation procedure has proven to be the most efficient and long-lasting one (Yang et al., 2013). Therefore, the following section will focus on this procedure. Moreover, as you will discover in the General discussion, we believe the mechanisms underlying neglect rehabilitation through PA might also be involved in saccadic adaptation, which could constitute a rehabilitation procedure as efficient as PA, if not more.

In the PA paradigm the relationship between the sensory vector and the motor vector sent to the arm is modified thanks to a visual shift elicited by prismatic goggles. This sensorimotor adaptation paradigm leads to an after-effect of a shifted arm pointing movement. The progressive modification of the arm movement is thought to rely on cerebello-cortical interactions, as proposed by Pisella et al. (2005). In their model, the cerebellum ipsilateral to the visual deviation inhibits the posterior parietal cortex contralateral to the prismatic deviation, a cortical involvement which could account for the effects of

PA on spatial cognition. In other words, in neurotypical control subjects, rightward PA would impact the right cerebellum which will in turn exert an inhibition on the left PPC, biasing attention orienting in favor of the left hemifield. In NP, a similar bias of attention orienting, but this time induced by leftward PA, would help compensate the neglect symptoms. Indeed, in neglect patients, performance in spatial attention tasks improves after rightward PA (Jacquin-Courtois et al., 2013).

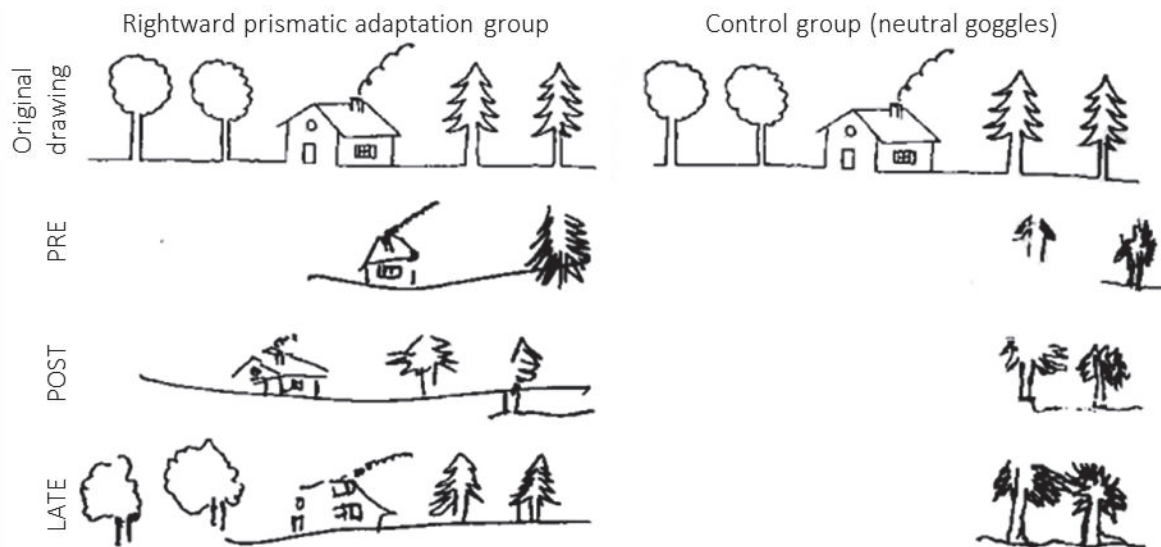


Figure 32: Benefit of rightward prismatic adaptation on neglect symptom. *Left panel: drawing performance of one representative neglect patient (NP) of the Rightward Prismatic Adaptation (RPA) group before (PRE), immediately after (POST) and 2 hours later (LATE). Right panel: drawing performance of one NP of the control group (neutral goggles) (adapted from Rossetti et al., 1998).*

This model is embedded in the theory of the interhemispheric imbalance (Kinsbourne, 1987; Corbetta et al., 2005; Pisella et al., 2006). This interhemispheric inhibition has been proposed to be underpinned by the inhibitory neurotransmitter γ -Aminobutyric acid (GABA) that is thought to support the generation of gamma oscillations (for review: Bartos et al., 2007).

Finally, leftward PA is known to produce neglect-like behavior in healthy subjects. Interestingly, Martin-Arévalo et al. (2016a) showed that after leftward PA, the cue-locked N100 was affected and asymmetries between the two hemisphere were observed. Moreover, leftward PA has been causally involved in IHI, since it impaired hemispheric imbalance (Figure 33) which was reflected in pseudo-neglect behavior (Schintu et al., 2016; Martin-Arévalo et al., 2016b).

Although much less investigated than PA, we suggest that SA might also rely on cerebello-cortical interactions. Indeed, SA and PA are visuo-motor plasticity processes which both affect cognition and both involve the cerebellum (e.g. Desmurget et al., 1998 for SA, Pisella et al., 2005 for PA). In addition, clinical observations suggest that SA relies on a cerebello-cerebral dialogue initiated by the cerebellum and subtended by the cerebello-thalamic tract (Gaymard et al., 2001; Zimmermann et al., 2015). **One working hypothesis of this PhD work was that SA could be a potential rehabilitation procedure for neglect symptoms. An ongoing study has been designed to test the effect of SA on these symptoms.**

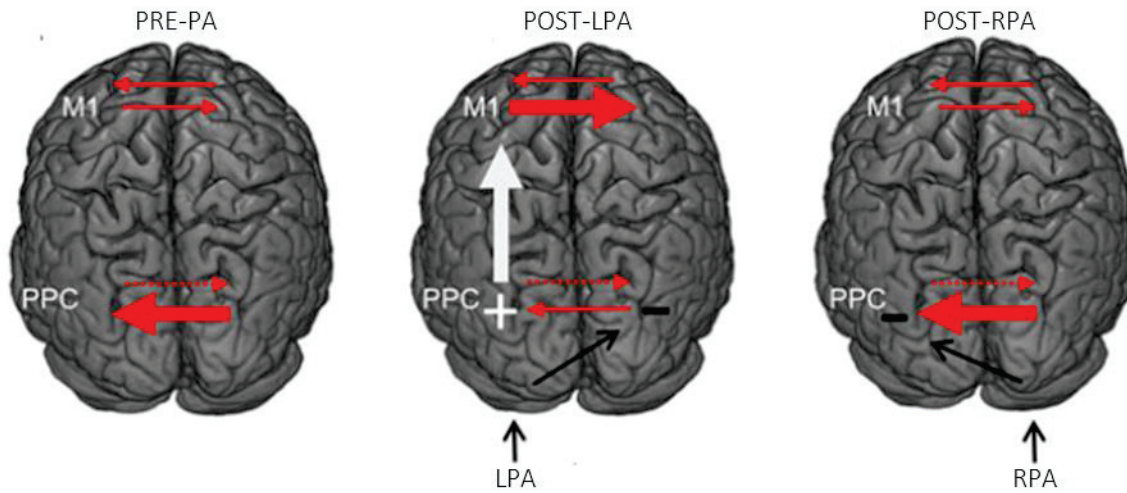


Figure 33: Prismatic adaptation effect on inter-hemispheric inhibition mechanism as proposed by Martin-Arévalo et al. (2016b). Black arrows represent the action of Prismatic Adaptation (PA) as proposed by Pisella et al. (2006). Red Arrows represent Inter-Hemispheric Inhibition (IHI). **Left panel:** Interhemispheric imbalance before PA. **Middle panel:** leftward PA (LPA) mimics the right brain damaged observed in Neglect Patients (NP). LPA decreases right-to-left IHI, thus increasing left PPC excitability. LPA would additionally increase excitatory intra-hemispheric connections in the left hemisphere between PPC and the primary motor cortex (M1) (white arrows in the scheme). The IHI would be consequently increased from left-to-right at M1 level. **Right panel:** rightward PA (RPA) inhibits the left PPC. However, the left PPC does not inhibit the right counterparts (Koch et al., 2011). Therefore, no change of IHI nor of the right PPC excitability is observed.

4. Oculomotor space and spatial cognition

Spatial cognition relates to the representation of the surrounding visual space that the brain uses to produce adequate behavior. It relies on cognitive maps that contain precise coordinates of objects in external space, but also of our body in relation to these objects. It has consequently been proposed that these maps are structured by sensorimotor processes since they are constantly updated by sensory inputs providing information to the motor system that, in turn will use them to get new sensorial inputs. (O'Regan and Noë, 2001; Zimmermann and Lappe, 2016; Collins et al., 2007a; Gremmler et al., 2014). **In the following section, we will review the evidence that support this theory and in which the current PhD work is partially anchored.**

4.1. Saccades and perception

Saccades and perception are tightly linked in the sense that the former bring the fovea, where the best acuity is achieved, onto objects of interest and therefore allows an enhanced perception. However, saccades involve that the retinal image jumps every time we move our eyes. Therefore, to perceive objects at the same position in space, remapping processes are needed. Moreover, to avoid vision to be blurred during saccades, the threshold of detection has to be increased. Due to this saccadic suppression phenomenon, intra-saccadic visual input cannot be used to resolve perturbations of the visual environment which can possibly occur during saccades. Rather, a comparison of visual inputs between stable pre- and post-saccadic ocular fixations is required. Given the limits of the saccadic remapping process on which this comparison relies, small changes of visual locations go unnoticed, a phenomenon called saccadic suppression of displacement.

4.1.1. Saccadic suppression : intra-saccadic impairment

This phenomenon corresponds to a reduction of visual sensitivity during saccades, in other words saccades lead to an elevation of perceptual threshold for visual stimuli presented during the intra-saccadic period. Bridgeman et al.'s (1975) reported that subjects failed to detect stimuli displaced during saccades. This result implies that the saccadic suppression (threshold elevation of detection) also impacts, to some extent, the remapping processes occurring during saccades. However, contradictory results exist on the extent of saccadic suppression. Some studies found weak or no threshold elevation while other found drastic impairment of perception (see for review: Ross et al., 2001). Campbell and Wurtz (1978) argued that this reduced sensitivity was due to the rapid motion of the retinal image. Burr and Ross (1982) indeed reported that, when stimuli move at saccadic velocity in condition of eye fixation, detection of high spatial frequency gratings is impaired, yet gratings with low spatial frequency are better perceived (Burr and Ross, 1982). This sounds a little bit counterintuitive. Indeed, high spatial frequencies relate to fine details while low spatial frequencies relate to broader visual zones or backgrounds such as landscapes for example. In ecological situations, a constant landscape is not interesting to be seeable during a saccade while details are much more relevant to track even during saccades. And actually, when real saccades occur, *i.e.* not simulated by moving stimuli at saccadic velocity, this is what is found: Burr et al. (1994) investigated the contrast sensitivity function of gratings that were briefly flashed during saccades and found that saccadic suppression is selective for patterns

modulated in luminance at low, but not high, spatial frequencies (Figure 34, top). They suggested that this pattern of results could be accounted for by a specific suppression of the magnocellular pathway during saccades. Burr et al. (1994) suggested that saccadic suppression could occur as early as the LGN in the visual pathway. It has long been proposed that one component of this phenomenon is mediated by the corollary discharge of the saccadic oculomotor commands (the other component, which dominates in natural conditions, is a masking of intrasaccadic visual inputs by pre- and post-saccadic stable retinal inputs). Berman et al. (2017) proposed that such a corollary discharge is produced by the intermediate (saccade-related) layers of the SC, and is transmitted to the middle temporal gyrus and the FEF through the pulvinar and the medial dorsal nucleus of the thalamus respectively (Figure 34, bottom).

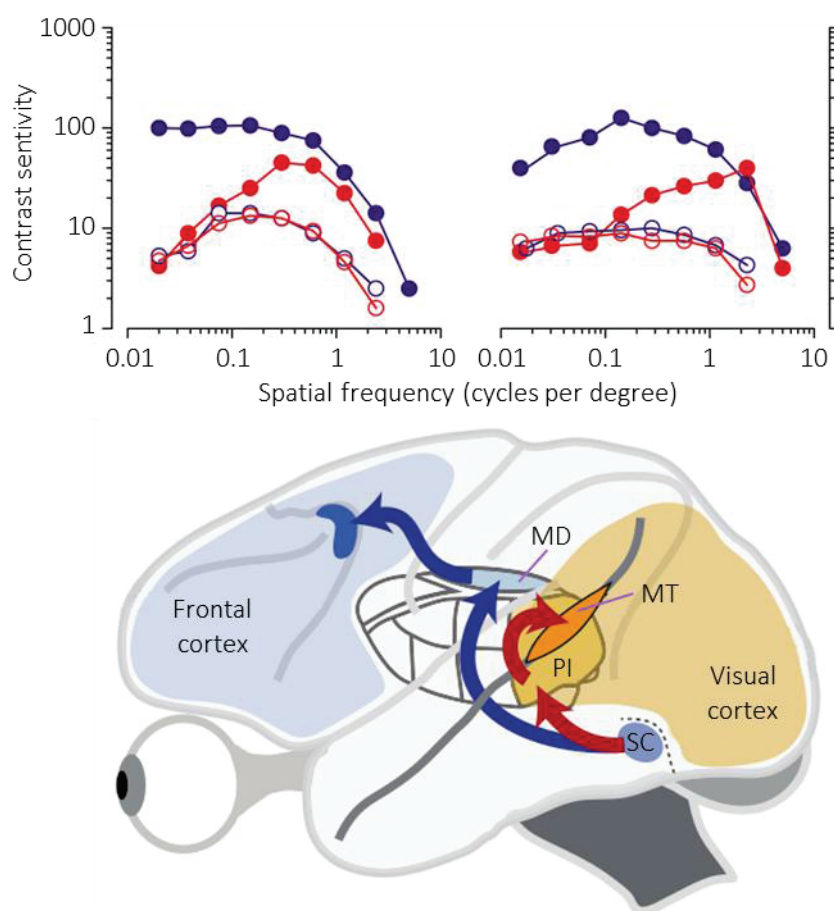


Figure 34: Specificity of the saccadic suppression phenomenon and cortical substrates of corollary discharge transmission to cerebral cortex. **Top panel:** Contrast sensitivity function in two different subjects. Blue dots: measured during fixation; red dots: during large horizontal saccades. Open circles: equiluminant colour modulation; filled circles: luminance modulation (adapted from Ross et al., 2001); **Bottom panel:** Putative corollary discharge circuit in the monkey brain. SC = Superior Colliculus; PI = Pulvinar; MT = Middle Temporal visual area; MD = Medial Dorsal thalamus nucleus (adapted from Berman et al., 2017)

4.1.2. Remapping across saccades

When we explore a visual scene, we alternate between fixations (during which vision is occurring) and saccades (during which perception is strongly impaired). Therefore, what V1 receives is a train of

snapshots of the visual scene taken from different viewpoints. To reconstruct a stable representation of the visual environment, the eye positions (viewpoints) and corresponding retinal images (snapshots) have to be combined together and have to be integrated across saccades. This spatio-temporal integration process is critical for maintaining perceptual stability. One first hypothesis proposed to account for this visual constancy phenomenon is the updating of the retinotopic maps, centered on the fovea, in which the visual world is represented. Duhamel et al. (1992) discovered neuronal mechanisms that could account for this hypothesis. Indeed, some neurons in the parietal cortex discharge in anticipation of a stimulus falling into their receptive field after an upcoming saccade (neurons of this type have later been found also in the FEF, the SC, and in several peri-striate visual areas). For this anticipatory shift of the RF to occur, neurons have to integrate the amplitude and the direction of the upcoming movement, namely, they have to integrate the saccade CD. This saccade CD is thought to be provided to the FEF by the SC through the medial dorsal thalamus nucleus, as proposed by Sommer and colleagues based on a series of electrophysiological recordings and pharmacological inactivation studies of the SC-MD-FEF pathway in the monkey (see review in Sommer and Wurtz, 2008).

A slightly different hypothesis has been proposed by MacKay (1972). The transsaccadic memory hypothesis posits that the world is assumed to be stable across a saccade unless there is evidence to reject that assumption. This approach can be framed into the Baye's theorem of optimal inference. The idea is that the locations of objects surrounding the saccadic target are stored. After the saccade, if these objects show the same locations relative to the fixation point, then the assumption of a stable world is correct. This hypothesis has been supported by works of Deubel and colleagues (Deubel, 2004; Deubel et al., 2002). In this framework, one can assume that the only important region is the one surrounding the future saccadic target. Moreover, it is known that the visual processing is enhanced around the saccade landing position which is referred to as the pre-saccadic shift of attention (Deubel and Schneider, 1996; Hoffman and Subramaniam, 1995; Kowler et al., 1995). This set of studies raises the idea that to maintain visual constancy only the part of the visual field surrounding the next saccade landing position is attended, kept in memory and updated.

Still another hypothesis posits that the brain contains spatiotopic maps representing the world in spatial coordinates. Positions in these higher order spatiotopic maps are updated after each new retinal image. This calibration hypothesis has been proposed by Bridgeman et al. (1994). Neuronal correlates of the spatiotopic update could be the gain field neurons and the real position neurons. Gain field neurons have activity which defines retinotopically-coded RF but which is modulated by the eye position (Andersen and Mountcastle, 1983). The integrated activity of several gain field neurons is thought to provide the activity of the real position neurons which RF is encoded in 'absolute' coordinates (*i.e.* egocentric- or world-based). While gain fields neurons have been identified in several cortical areas including the parietal cortex, the FEF, the SEF and the dorsolateral PFC, real position neurons have been found much more inconsistently (Galletti and Fattori, 2002). Thus the spatiotopic map hypothesis has received less experimental evidence than the other hypotheses relying on retinotopic maps.

However, the spatiotopic maps hypothesis better fits with our subjective experience of the world, namely the world is perceived as a whole and not as series of retinal images. Note, that these different coding schemes are not exclusive, and it might be that the retinotopic maps are updated through the pre-saccadic RF shifts and then in turn updated into spatiotopic maps.

At the behavioral level, one way to test visual constancy across saccade is by asking subjects to localize targets flashed before the saccade onset. And even though we feel that the visual space is stable, at a finer grain, it might not be the case... but no spoilers; it's coming right in the next section.

4.2. Saccades, saccadic adaptation and localization

4.2.1. Saccades and localization

One drastic impact of saccades on localization is the peri-saccadic compression phenomenon. Early work in the 60's already investigated this phenomenon but Ross et al. (1997) reported the princeps study on that topic. The take home message of this study is that probe stimuli flashed around the time of the saccade onset are mislocalized. This shift is not of constant size or direction for different positions in the visual field but rather results in a compression of space towards the saccade target position (Figure 35). Morrone et al. (1997) replicated these results and showed that this compression appears in a window of 150 ms before the saccade to 150 ms after, the mislocalization being maximal at the time of saccade onset. The size of this shift can be up to half of the saccade amplitude. In this study, the localization performances were compared in two conditions: (1) concomitant with real saccades and (2) concomitant with simulated saccades (*i.e.* the eyes were immobile and the visual field moved at the saccade velocity). Whereas a compression was found with real saccades, no compression occurred in the latter condition. These results argue against the idea of visual motion suppression being entirely responsible for that phenomenon. For these authors, the peri-saccadic compression could arise from the combined activity of three neuronal populations: neurons with anticipatory discharge, neurons that only discharge for pre-saccadic position, and neurons that discharge for both. The activity of these populations is transmitted to higher order areas that might interpret the probe and the saccadic target to be at the same position (Ross et al., 2001). Although appealing, the peri-saccadic compression phenomenon and its putative neuronal correlates was challenged by Lappe et al. (2000) who found that peri-saccadic compression occurs only when post-saccadic visual references are available. In the total absence of post-saccadic visual feedback, the mislocalization becomes a constant shift, *i.e.* always occurs in the direction of the saccade (a phenomenon well described before by Honda and others: *e.g.* Honda, 1991). This could result from a change of reference: either an egocentric one (no visual references available) or an allocentric one.

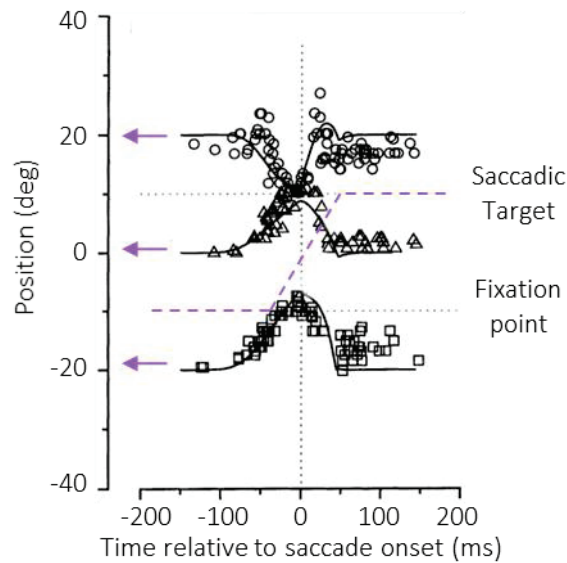


Figure 35: Peri-saccadic compression of space. Reported position of flashed target in function of their presentation time relative to the saccade onset. Purple arrows indicate the real position of the flashed targets (adapted from Ross et al., 1997).

4.2.2. Localization after SA

One way to test whether space representation is structured by oculomotor mapping is to change the metric of saccades and study the effect of these metric changes on the ability to localize in the visual space. Probe stimuli to be localized are presented either concomitantly with a saccade or not.

Several studies have reported an effect of SA on the localization performances. In the study reported by Awater (2004), subjects RS gain was adapted in both a backward and a forward fashion and in each case, the localization of bars flashed around the time of the saccade was tested. The results showed the classical peri-saccadic compression of space towards the saccade target before SA. More interestingly, post-adaptation measures demonstrated that this space compression was linked to the saccade landing position and not the actual visual saccadic target. The authors also reported that probe localization SA-induced shift was observed for targets flashed up to 200 ms before the saccade. Bruno and Morrone (2007) also investigated the effect of RS backward and forward adaptation on localization. In their study, subjects reported either verbally or by pointing with the hand. Their results showed that, in both cases, there was a mislocalization of the probe stimulus in the direction of the adaptation. In addition of providing evidence that SA recalibrates spatial maps, this study also suggests that such recalibrated spatial maps are shared by perception (verbal report) and action (hand pointing movement). Collins et al. (2007a) interestingly compared the amount of the SA-induced mislocalization with the adaptive field described earlier (see the adaptive fields in the Effect on saccade characteristics section, 2.2.4.2). The saccades were elicited with an overlap paradigm, namely, the fixation point and the saccadic target were simultaneously displayed and the saccade had to be initiated when the fixation point turned off. This paradigm was supposed to elicit VS, however, the mean saccade latency they reported matches the latency of RS. Concerning the adaptation fields, they replicate the classical findings (Figure 15). At last, comparing localization performances for probe stimuli randomly flashed at positions inside or outside the adaptation field, they showed that the spatial pattern of mislocalization (Figure 36) resembles the spatial transfer of adaptation to other saccades around the adapted position, *i.e.* the

adaptation field. Again, this similar effect of SA on other saccades and on probe stimuli provides empirical evidence for shared spatial maps between action (saccades) and perception (localization). Similar results were found by Schnier et al. (2010) and extended to forward adaptation which was not investigated by Collins et al. (2007a). Zimmermann and Lappe (2009) investigated the effect on probe localization of both RS and VS backward adaptation. The probe stimuli could be either flashed just before saccade initiation or displayed for more than one second before saccade onset. They report that RS adaptation led to a mislocalization of flashed probe stimuli whereas VS adaptation led to a mislocalization of both flashed and stationary probe stimuli. The effect of adaptation on localization have been confirmed in non-human primates by Gremmler et al. (2014). These results further suggest that the shared representation between action and perception follows the partial segregation of saccadic types. Finally, Schnier and Lappe (2012) studied the backward and forward SA-induced mislocalization of stationary and flashed targets. They found that the mislocalization of stationary targets is bigger than the one of flashed target after forward RS adaptation. Both types of targets were mislocalized after forward SA and after backward SA but the former induced a bigger mislocalization.

Taken together the results of these studies suggest a common spatial representation for action and perception. However, in all these studies, subjects perform the localization task concomitantly with the adapted saccade. A justified concern can therefore be raised. Indeed, the shift of the localization might emerge from the mismatch between expected landing position (saccade target) and actual landing position of the eyes which would imply that the localization is performed by comparing the remembered position of the probe stimulus and the landing position of the eye. To test whether SA induces a distortion of visual representation, localization performances should then be tested in absence of saccade. Of course, I was not the first one to raise this concern and studies have already investigated probe localization after SA with the eyes fixating. We will focus here on those studies not involving allocentric localization and which thus highlight *raw* perceptual maps not anchored to any reference in the visual space. Zimmermann and Lappe (2010) investigated RS backward and forward SA elicited either with the classical double-step paradigm (ISS size= 3°) or with the constant-error paradigm (three ISS sizes tested in separate sessions: 1°, 2°, and 3°). They then studied the probe localization performances with the eyes immobile. They found that with the classical paradigm, only forward adaptation induced a shift in the localization in the direction of adaptation. With the constant-error paradigm, they found that the three ISS sizes of the forward adaptation induced a shift of the localization. Interestingly, the shift was not related to the size of the ISS. Regarding the backward adaptation, only the 3° ISS induced a shift of the localization in the direction of the adaptation. They concluded that the saccade motor parameters have an implication in visual space perception. The study of Schnier and Lappe (2012) presented above, also investigated the mislocalization with the eyes immobile. In this condition they found that only forward adaptation led to mislocalization of stationary and flashed targets. Another piece of evidence was brought by Garaas and Pomplun (2011). In their study they investigated forward and backward adaptation of both vertical and horizontal VS, after which subjects were asked to judge the length of the vertical or the horizontal line of a cross continuously centrally presented. They found that the backward adaptation of horizontal saccade induced an underestimation of the horizontal line length whereas forward adaptation of horizontal saccade induced an overestimation of the horizontal line length. They found similar results for the vertical adaptation which impacted, in this case, the judgment of the vertical line length.

Thereby, this set of studies provides stronger argument to the idea of a visual space shaped by oculomotor parameters. However, the mechanisms underlying the recalibration of the maps of the

external world are still poorly understood. For example, the finding of Zimmermann and Lappe (2010) highlighting a similar shift after SA induced by different ISS sizes is intriguing. Indeed, if SA induces recalibration of space, why would not this recalibration be parametric? Also, even though we know that backward and forward adaptation are different mechanisms, why would the latter impact more the mislocalization, especially that we know that backward adaptation is faster, stronger and more robust than forward adaptation?

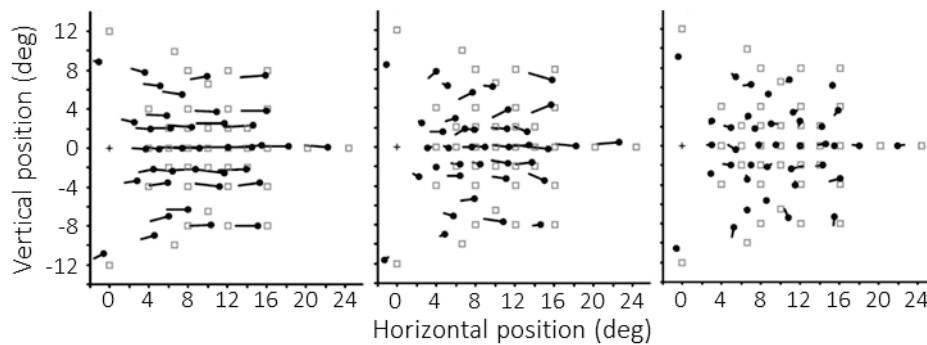


Figure 36: *Effect of backward saccadic adaptation of rightward voluntary saccades on localization judgments.* The targets were flashed before the initiation of the saccade at positions (squares) inside or outside the adaptation field. The heads of the vectors (dots) represent mean localization before saccadic adaptation (SA) and the tips represent data after SA. **Left panel:** with visual references at the end of the saccade; **Middle panel:** without visual references at the end of the saccade; **Right panel:** with the eyes kept at the fixation point (adapted from Collins et al., 2007a).

4.3. Saccades, saccadic adaptation and other motor effectors

4.3.1. Head movements

4.3.1.1. Gaze shifts

In the laboratory, we usually study the orientation of the line of sight with the head still. Yet, in natural situation, orientation of the line of sight is a combination of eye, head, and even body movements. The direction of the line of sight in space, or gaze, is indeed the sum of the eye-in-orbit, head-on-trunk and trunk in space positions. Here we will only focus on the rapid gaze shifts (eye-head saccades) but this coordination of eyes and head is involved in many behaviors such as eating for example. Similar to eye saccades, gaze shifts serve to bring the image of an object on the fovea. They also serve to explore parts of the visual scene that are not available in the oculomotor range. Actually, saccades occurring without head movements rarely exceed 15° in amplitude (Bahill et al., 1975). When eye-head movements are elicited, the head movement corresponds to 80% of the total gaze shift (Becker, 1989) (Figure 37). Accordingly, Morasso et al. (1973) showed in monkeys that the eye-in-head saccade corresponds to a normal saccade from which the signal corresponding to the concomitant head movement has been subtracted thanks to the vestibulo-ocular reflex. However, nowadays, it is admitted that the desired gaze shift emerges from a decomposition in separate commands for the oculomotor and the cephalomotor system (Pélisson and Guillaume, 2009). In reaction to the sudden appearance of a

stimulus in the visual space, the eye saccade latency is usually of 200 ms and precedes the head movement by 20-50 ms. When the gaze shift is towards a predicted target, the pattern reverses, the head starts to move before the eyes. Finally, when subjects move their gaze at their own pace, eye- and head-movements are synchronized (Leigh and Zee, 1999). The kind of head movements accompanying eye saccades have a ballistic nature and are controlled by an internal feedback (Pélisson and Guillaume, 2009). Interestingly, just like eye saccades, ballistic head movements can be adapted (Gauthier et al., 1986).

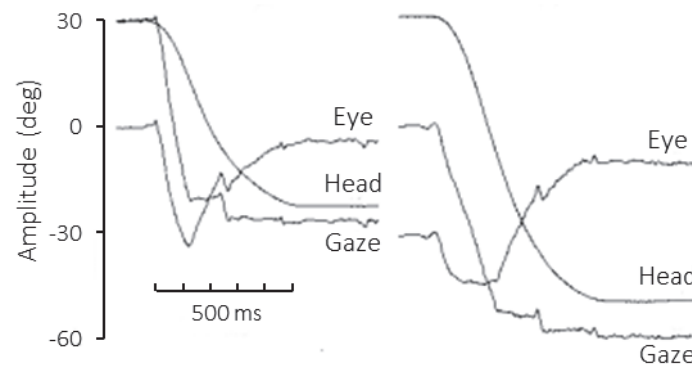


Figure 37: Gaze shifts. Gaze is the summation of the eye-in-head position and head position. The head starts at 30° to the right and the eye has an orbital eccentricity of 30° (therefore at the center of the screen). **Left panel:** Target step of 60° starting at 30° of eccentricity. **Right panel:** Target step of 60° starting at 0° of eccentricity (adapted from Becker, 1989).

4.3.1.2. After SA

Since the motor system is able to adapt, it is interesting to question the transfer of SA to gaze shifts (*i.e.* eye-head combined). One study reported that there was no transfer of backward RS adaptation to head movements elicited by a verbal command nor to head movements elicited by the sudden appearance of a peripheral visual target (Kröller et al., 1996). Conversely, Cecala and Freedman found a transfer of gaze adaptation to head movements in monkeys (Cecala and Freedman, 2008) and in human (Cecala and Freedman, 2009). However, these two later studies adapted gaze shifts performed with head unrestrained, therefore, the transfer from SA to head movements cannot totally be disentangled. These studies however suggest that the gaze adaptation takes place upstream from where eye movements and head movements are segregated. Taken together these results suggest that there is a common site for the generation of the eye- and head-movements and that only acting on eye-movements has consequences on the combination of these two motor effectors.

4.3.2. Hand pointing movements

4.3.2.1. Link with saccades

When we perform a goal-directed movement with the arm, the visual system supplies the hand motor system with signals of the position of the goal. As the accuracy of such signals relies on the saccadic

foveation of the arm goal, the coordination between arm and eye movement is important to achieve optimal reaching performance. The eyes usually land on the target at the time the arm starts to move, yet the two motor commands (eyes and arm) are programmed in parallel (Desmurget, 1998). Visuospatial attention might be the dedicated coordinative mechanism (Pélisson and Prablanc, 2009). When studied separately, these two movements are always preceded by a shift of visual attention towards the goal of the movement (Schneider and Deubel, 2002). Moreover, the gaze stays anchored to the target until the hand movement completion, suggesting that no other shift of attention can occur (Neggers and Bekkering, 2000; Neggers and Bekkering, 2001). It has also been shown that the hand pointing movement (HPM) accuracy is impaired when the eyes are not allowed to move towards the target. The eye-hand coupling is also supported by neurophysiological data collected at the level of the cerebellum for visuo-manual tracking task (Miall et al., 2001). At the cerebral level, the PPC seems to play a major role in this coordination (Pélisson and Prablanc, 2009). The PPC contains gain field neurons for eye movement (see Remapping across saccades section) and also for arm movements (Andersen et al., 1997). Moreover, the PPC is involved in attentional shift (see Stripping the orienting system: neural substrates section 3.3).

4.3.2.2. After SA

These eye-hand coordination substrates are also key nodes of potential SA sites. Therefore, it is reasonable to investigate the effect of SA on HPM. However, studies investigating this transfer are sparse. Concerning RS adaptation, de Graaf et al. (1995) induced backward SA and then tested whether SA affects the size of HPM performed without saccade. They found that the endpoint of hand pointing movements shifted in the direction of the SA (transfer of 30%). Kröller et al. (1999) performed backward adaptation of gaze movements (head and eye combined). They found a small but significant transfer of adaptation to HPM performed without gaze movement (to a single target: 15.2% of transfer; to a sequence of three targets: 18.5% of transfer) and a larger amount of transfer to HPM performed with gaze movements (53%). In this study they also investigated forward gaze adaptation, however, this condition did not reveal significant transfer to HPM. Moreover, Hernandez et al. (2008) found a modification of HPM towards sustained target but not towards flashed target after backward SA. This modification was, however, in the opposite direction of SA. In the condition of forward adaptation, the pattern was reversed, SA transferred to HPM towards flashed target but not towards stationary target. The transfer was in the same direction as SA in this condition. Aside these studies, others have failed in revealing such a transfer (Mclaughlin et al., 1968). Cotti et al. (2007) did not highlight a significant transfer of RS adaptation to HPM (Figure 38). However, this study also investigated VS adaptation and disclosed in this case a significant transfer to HPM towards a single target (transfer of 32.9%) and towards sequence of targets (43.3% and 46.6% depending of the adapted vector).

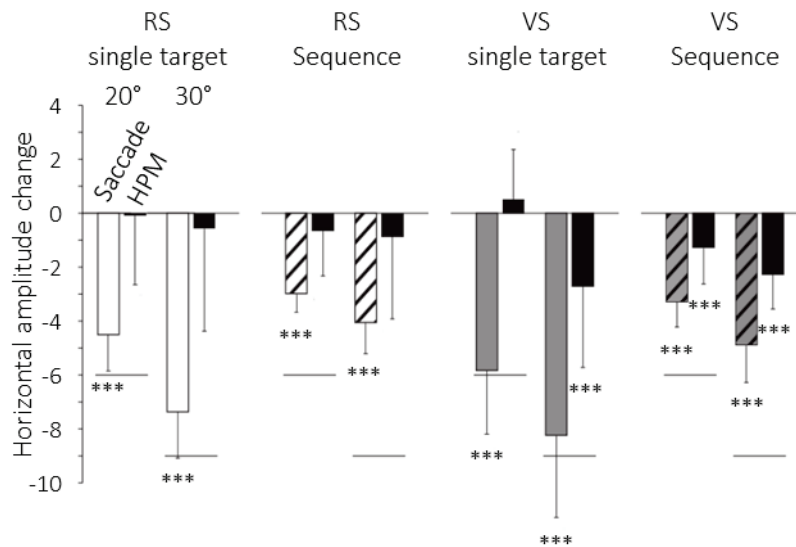


Figure 38: Effect of saccadic adaptation on hand pointing movement. Bars represent the relative change of amplitude between pre- and post-exposure to either RS or VS adaptation for saccade (first bar of each condition) and for Hand Pointing Movements (HPM; second bar of each condition). The adapted saccade could be either of 20° or 30° of eccentricity. There were two different saccadic tasks, either involving a single saccade or a sequence of saccades. The horizontal lines at -6° and -9° represents the level of changes corresponding to 100% SA after-effect (in case of saccadic task) and SA transfer (in case of HPM) (adapted from Cotti et al., 2007).

4.4. Saccades, saccadic adaptation and attention

Visual maps re-alignment is not the only consequence of SA. Indeed, SA has been proved to be tightly linked to visuospatial attention. This is the topic of the present section.

4.4.1. Pre-saccadic shift of attention

It has been shown that when a change occurs somewhere in the visual field, it first attracts one's attention, and, a bit later, one's gaze. Saccades cannot be made without such pre-saccadic shift of attention. Indeed, in their princeps study using a dual task (saccade and discrimination), Deubel and Schneider (1996) showed that when the target to be discriminated and the saccadic target share the same spatial position, the performance of discrimination, taken as a proxy of attentional focus/resource, increases as compared to when these two targets are spatially distinct (see Hoffman and Subramaniam, 1995 for similar results). Moreover, Kowler et al. (1995) showed that saccades towards a location at which the attention focus is attracted, are faster and more accurate. They found the same results as Deubel and Schneider's (1996) results concerning the enhanced discrimination performance at the saccade target location as compared to other locations. Lastly, they attempted to dissociate the locus of attention and the saccadic target, but no evidence was found to support this possible dissociation. However, later studies showed that attentional focus can be divided. Indeed, Godijn and Theeuwes (2003) showed that in a sequence of two VS, attentional performance increased at the two saccade landing positions as compared to any other locations. These results suggest that when the parallel programming of saccades occurs, attention can shift simultaneously to two different locations. Doré-Mazars et al. (2004) showed that attentional focus can shift away from the saccadic target location

during the saccade latency period, yet 60ms before the saccade initiation, attentional focus is obligatory linked to the saccadic target location (see Deubel, 2008 for similar results). Interestingly, Deubel and Schneider (2003) showed that when the saccade is delayed, attentional shifts still occurs immediately before the saccade initiation. They also showed a distinction with ballistic arm reaching movements for which it was not the case, suggesting a privileged link between spatial attention and eye movements.

This privileged link between eye movements and visuospatial attention is part of the premotor theory of attention predictions. This theory considers that covert shifts of attention (eyes immobile) are identical to overt shifts of attention, *i.e.* saccades, which have been planned but not executed due to inhibition at the oculomotor output level (Rizzolatti et al., 1987; Smith and Schenk, 2012). The premotor theory of attention emerged in part from the failure to identify any neural substrates specific of spatial attention. Therefore, it was postulated that spatial attention is generated by planning and executing actions, namely that spatial attention is the consequence of activation of the motor system. The premotor theory of attention can be summarized by four main principles:

- (1) Attention and motor planning use the same neural substrates, thus attention is a consequence of neuronal activation in the motor maps.
- (2) Covert shift of spatial attention is functionally equivalent to motor planning which, therefore, is both necessary and sufficient to shift attention.
- (3) Spatial attention can be activated by any effector system engaged in goal-directed motor behavior;
- (4) Among these effectors, the oculomotor system has a privileged link with visuospatial attention, implying that if there is a competition between motor effectors for the allocation of visuospatial attention, the eye-movement goal should be favored.

4.4.1.1. Shared neural substrates prediction

On a first glimpse, it is easy to draw the conclusion that oculomotor system and attention share the same neural substrates (Figure 39). Indeed, neuroimaging studies have demonstrated that a fronto-parietal network is activated while preparing an eye movement and while covertly shifting attention (Corbetta, 1998; Nobre et al., 2000; Beauchamp et al., 2001; de Haan et al., 2008). Also, studies have highlighted that TMS applied at the level of the FEF yields similar perturbation effects on both saccades (Beckers et al., 1992; Müri et al., 1996; Thickbroom et al., 1996; Zangemeister et al., 1995) and attention (Grosbras and Paus, 2002; Smith et al., 2005). Moreover, two studies used microstimulation of the saccade-related neurons of the FEF to investigate its consequences on attention. Using stimulation intensities below the threshold of saccade elicitation, they observed that although the eyes stayed immobile, there was a covert shift of spatial attention in that discrimination performance at the location where the non-elicited saccade should have landed (saccade-related neurons motor field) was higher than for other locations (Moore et al., 2003; Moore and Fallah, 2004).

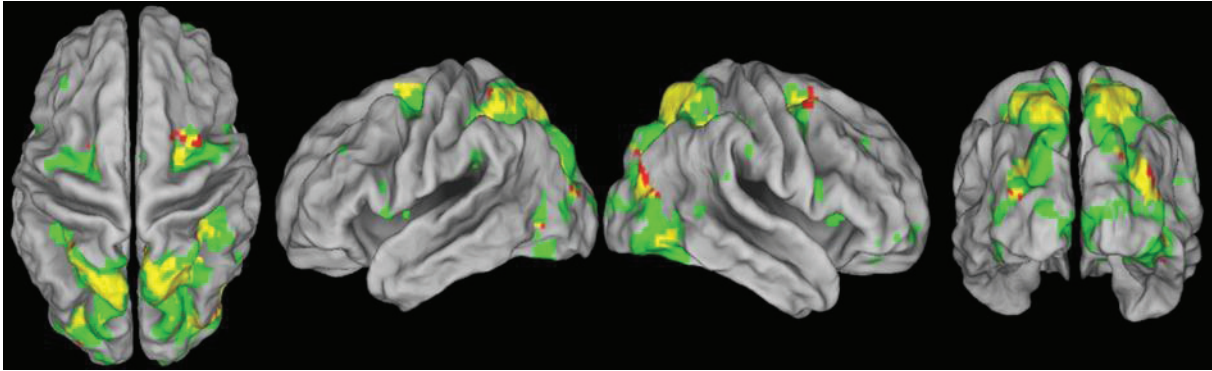


Figure 39: Overlapping networks of covert and overt shifts of attention. Red: significant activity during covert shifts of attention. Green: significant activity during overt shifts of attention. Yellow: significant activity during both covert and overt shifts of attention (adapted from de Haan et al., 2008).

However, the story does not end here. Indeed, neuronal populations specifically dedicated to either spatial attention or to saccades do exist (Thompson et al., 1997; Sato and Schall, 2003; Thompson et al., 2005). Moreover, Eimer et al. (2007) claimed that they managed to elicit separately shift of covert attention, overt shift of attention (called combined task) and pure line of sight shift not involving attention while recording EEG activity. In order to elicit differentiated attentional and eye shifts, their experiment comprised 3 conditions: (1) the attentional shift, (2) the combined shift, and (3) the eye shift. Each trial was composed of a central cue (indicating the likely side of the target) and after a delay of 700 ms a visual target was presented (green LED for 'Go' targets, red LED for 'No-Go' targets). In the attentional shift task, the participants were instructed to pay attention to the cued side and answer vocally only when the target was a 'Go'. In the combined shift task, the participants were instructed identically but had to provide an answer with an eye movement only when the LED was a 'Go' target. In the eye shift task, participants were instructed to saccade towards the cued side regardless of the color of the LED only when the Go-signal was presented on either side. The probability of the 'Go' target appearing on the cued side was equivalent to the one of the un-cued side. This trick discouraged endogenous attentional orienting towards the cued side. Although debatable (the saccade direction is still known allowing *a priori* shift of attention), the evoked potentials related to these three types of shift were similar but different enough to suggest separate neuronal populations (Figure 40).

These ERP results as well as the limitation of the technique used in the studies presented in the preceding paragraph (both TMS and microstimulation activates extended neuronal populations) jeopardize the first prediction of the premotor theory of attention.

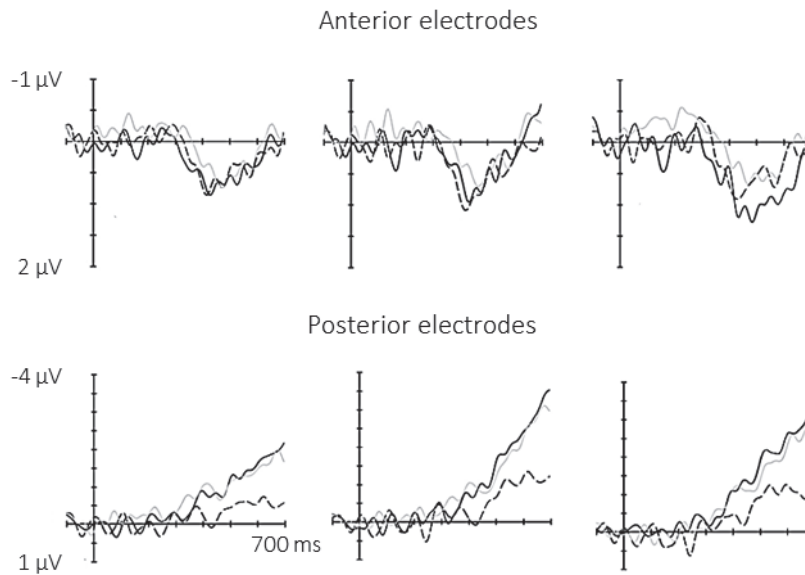


Figure 40: EEG responses for covert and overt shifts of attention during cue-target interval. Black solid lines: covert attention task. Black dashed lines: saccade task; Grey solid lines: combined task, namely overt shift of attention (adapted from Eimer et al., 2007).

4.4.1.2. Functional equivalence of motor planning and spatial attention

The premotor theory of attention posits that motor preparation is sufficient to elicit attention shifts. This assumption can be supported by studies investigating the pre-saccadic shift of attention. However, in these studies the modality of attention, endogenous or exogenous, was not explicitly questioned but the methods used strongly favored exogenous shifts of attention (except for Deubel's (2008) study in which the saccadic target and the discrimination targets were cued centrally). Also, the modality of the elicited saccade, voluntary or reactive, varied between studies. For example, Montagnini and Castet's (2007) study explicitly interrogated the endogenous shift of attention by manipulating the validity of the central cue. The central cue indicated both the saccade goal (always valid) and the attentional task target (either 25%, 50%, or 75% valid). Therefore, when the probability of having the discrimination target at the same location than the saccadic goal was low, subjects should endogenously orient their attention at the other location. The results are in accordance with this prediction, suggesting that when it comes to endogenous attention, it is possible to dissociate the saccadic goal and the attentional focus. Yet, the modality of the elicited saccade was not explicit. Targets were always displayed but the saccade 'Go' signal was the brief (and I mean very brief: 6.25 ms) appearance of the central cue. This cue indicated the saccade target and the probable location of the discrimination target. The saccade latencies were between 201 and 222 ms depending on the subject, more consistent with RS latencies than with VS latencies. Thus, if we postulate that RS were elicited in this experiment, while endogenous attention shifts were elicited then, it is possible that a dissociation of saccadic goal and attention focus can appear across modalities but not within the same modality (*i.e.* reactive/exogenous or voluntary/endogenous). However, Klein and Pontefract (1994) in an earlier work used the same approach of varying the cue probability and found similar results. The latencies of saccades they report in these studies are consistent with VS (>350ms).

These studies support the idea that motor preparation is sufficient, yet not obviously necessary for attention to shift. However, the necessity of motor preparation is one central characteristic of the premotor theory of attention. In contrast, the fact that motor preparation is sufficient can be explained in other frameworks such as the Selection-for-Action theory (Schneider, 1995; Schneider and Deubel, 2002) or the priority map hypothesis (Bisley, 2011).

And this is where it gets complicated for the premotor theory of attention. Indeed, neuropsychological data as well as experimental works have suggested that it does not hold true for endogenous attention (Smith and Schenk, 2012) because the latter does not require oculomotor preparation, as suggested by Montagnini and Castet's (2007) and Klein and Pontefract's (1994) studies. In patients, reported results consistently show a dissociation between, on the one hand, preserved endogenous attention orienting and, on the other hand, impairments of oculomotor behaviors and of exogenous orienting of attention (Henik et al., 1994; Smith et al., 2004; Rafal et al., 1988)². Note that the proponents of the premotor theory of attention suggest that patients are impaired at saccade execution but not at saccade planning. An interesting approach to rule out this possibility is, in healthy human subjects, to probe attention outside the oculomotor range, rendering saccade execution impossible but also saccade planning unlikely. Based on this procedure, Smith et al. (2012) presented their discrimination targets in the nasal hemifield, *i.e.* within the oculomotor range or in the temporal hemifield, *i.e.* inaccessible by eye movements. They showed that peripherally cued target did not benefit of attentional shift in the temporal hemifield whereas centrally cued targets did benefit of attentional shift even when saccades were not plausible.

From these studies, two alternative conclusions can be drawn: either the premotor theory of attention is restricted to the exogenous orienting of attention or the motor planning-attention link has to be conceptualized differently. Indeed, the reviewed literature presented here as well as the one we will present in the following section still supports the idea of a tight link between eye movements and attention.

4.4.2. Attention - SA coupling

As we have just reviewed, there are common mechanisms between attention and saccadic eye movements. However, these studies do not allow to determine the nature of this coupling. **This PhD work on the plasticity of saccadic eye movements was interested in the specific coupling between visuospatial attention orienting and saccadic adaptation.** Indeed, SA indirectly contributes to perceptual performance by optimization of eye scanning in visual search, which echoes the role attributed to attention. And quite interestingly, the cortical substrates of SA, which have been recently investigated (Gerardin et al., 2012), share with those of attentional orientation (Corbetta & Shulman, 2002; Corbetta et al., 2008) a marked endogenous *versus* exogenous segregation with both VS backward adaptation and endogenous attention involving the posterior IPS whereas RS backward adaptation and exogenous

² But see Blangero et al. (2010) : Single case study of a patient with right posterior (compared to a group of 4 control subjects). The task consisted in a letter discrimination with or without eye movements (overt or covert attention shifts respectively). The patient discriminated letters presented at 8° of eccentricity during overt shifts but performed at chance during covert shift. For both covert and overt shifts, letter discrimination was impossible at 2.5° of eccentricity

shifts of attention both recruiting the right TPJ. But, as for the premotor theory of attention, this anatomical overlap is not sufficient to claim a functional coupling. The strongest argument for a functional coupling between attention and SA would be the demonstration that these two processes can impact each other. This coupling can be considered in two directions: (1) the effect of attention on SA and conversely, (2) the effect of SA on attention. As a matter of fact, although sparse, evidence from recent studies supports this assumption.

4.4.2.1. Effect of attention

The saccadic gain has been observed to be modulated by errors produced by higher cognitive mechanisms than the classical bottom-up error signal. Schutz et al. (2014) designed a task in which subjects had to perform a perceptual discrimination. Each session was composed of a first perceptual task (100 trials) in which the target was presented at the fourth position of a six-letter string. This perceptual task was then followed by an *adaptation exposure* (300 trials) which consisted in the same perceptual task except that the target was presented at either a less eccentric position (backward) or a more eccentric (forward) position than in the initial perceptual task. They tested the size of RS performed during this perceptual task and demonstrated that RS gain decreased during the perceptual task involving the less eccentric target while it increased during the task with the more eccentric target. Khan et al. (2014) provided evidence that a salient distractor presented close to the saccadic target can induce saccadic gain changes. Varying the saliency of the distractor led them to show, in addition, that the more salient the distractor the more the saccadic gain change. They also tested distractor locations either less eccentric (backward) or more eccentric (forward) than the target and found, interestingly, that the decrease in gain was more robust than the increase in gain. This difference was also observed by Schutz et al. (2014) and echoed the difference between backward and forward adaptation types.

McFadden et al. (2002) were interested in knowing whether the covert shift of attention could be adapted. They designed an elegant study to answer this question. They measured the time to covertly shift attention using the illusory line motion (Hikosaka et al., 1993). Then, during a peripherally cued attention task, they stepped the peripheral cue during the shift of attention either backward or forward. They investigated separately the left and the right hemifield. They found that the focus of attention was shifted backward after backward steps of the peripheral cue and conversely, the focus was shifted forward after steps in the forward direction. This shift was also selective of the hemifield in which it was performed. Finally, they investigated the transfer to saccades and found a decreased saccadic gain after the backward shift of the peripheral cue during the covert attention task during which no eye movements were performed. The forward procedure did not transfer to the saccadic gain.

Lastly, Gerardin et al.'s (2015) study addressed the impact of attentional load on SA. They designed a double-task (SA and discrimination) in which the visual target used to induce SA was also a target to be discriminated. This target could be either easy or hard to discriminate, these two conditions differing only by the instructions provided to the subjects, and not by the stimulus properties which were indeed identical. In the left, adapted, hemifield, the target stepped backward during the saccade towards the target. The authors compared the modulation of the saccadic gain between the low demanding attentional task and the high demanding one. They also tested the modulation of VS gain before and after this leftward RS adaptation procedure. They found that the adaptation time course was faster when the adaptation procedure was coupled with the high demanding attentional task. In addition, both

the after-effect of RS adaptation and the transfer to VS were stronger after the procedure coupled with the high demanding attention task.

Therefore, this set of studies provides evidence for an effect of attention on SA. Attention can produce saccadic gain modulation even when no eye movements are required suggesting that the error signal leading to adaptation has to be selected by attentional processes as a relevant information. Quite interestingly, the last study presented here suggests that attentional load boosts SA and that the coupling between attention and oculomotor plasticity is not restricted to the spatial dimension.

4.4.2.2. Effect of SA

On the pre-saccadic shift of attention

The pre-saccadic shift of attention automatically unfolds towards the saccade's target just before saccade initiation (see Pre-saccadic shift of attention section, 4.4.1). Studies have investigated whether this shift is coupled to the visual target eliciting the saccade or the saccadic goal (*i.e.* saccade landing position). To do so, SA was used as an interesting tool allowing to dissociate the visual target and the saccadic goal by changing the saccade metric. A first study conducted by Ditterich et al. (2000b) showed that the attention focus remains linked to the visual target eliciting the saccade after SA. Therefore, after gain modulation, the attentional focus and the saccade landing position are no longer spatially congruent. However, it seems functionally counter-productive to dissociate the pre-saccadic of attention and the saccadic landing position in ecological situation. And indeed, Doré-Mazars and Collins (2005) investigated this matter using a concomitant discrimination and RS task and found results which clearly contradict Ditterich et al.'s (2000b) conclusions. Subjects were presented a visual scene comprising five placeholders. During the saccade preparation, the target was briefly flashed in one placeholder. The visual scene was stepped backward during the subsequent saccade. They showed that after SA the location of the best discrimination performance corresponded to the saccade landing position and not to the visual saccadic target. In another study, these authors also questioned this matter for VS adaptation (Collins and Doré-Mazars, 2006). They replicated their results concerning RS adaptation and showed that even for VS the attention focus is coupled to the saccadic goal and not the visual target eliciting the saccade. Finally, Khan et al. (2010) tackled this question through a different approach. It is known that presenting an irrelevant cue shortly before the initiation of a target-directed saccade shortens its latency (Kowler et al., 1995). Therefore, they adapted saccades and flashed cues either at the visual target location or at the new landing position of the saccade which amplitude has been modulated by SA. They found that saccade latency decreased when cues appeared at the new landing position of the saccade and not at the visual target location.

These results hence argue that the pre-saccadic shift of attention is based on the motor command of the movement to be performed. This conclusion is also in line with a study using pro- and anti-saccades showing that the pre-saccadic shift is linked to the saccadic goal not to the target eliciting it (Mikula et al., 2018). The negative results reported by Ditterich et al. (2000b) can be due to the protocol itself. In this study, the visual target eliciting the saccade was composed of two short lines situated parallel to, one above and the other below, the horizontal meridian, and subjects had to aim at the empty space in between the bars. The discrimination target was on the horizontal meridian and at the same horizontal eccentricity as the target. It is possible that this design produced noise (because of the lack of visual feature to land on) and masked the results of the coupling of the pre-saccadic of attention and the

saccadic motor goal. In addition, and more critically, they only used 50 trials in their adaptation procedure, which is enough to reach the asymptote but maybe insufficient to consolidate a sustainable after-effect of SA.

On attentional performances

The initial aim of Wick et al. 's (2016) study was to investigate the spatial extent of the attention field after SA using a flanker task. In this task, the discrimination target is '*flanked*' by distractors. The closer the distractor from the target, the greater the interference which results in an increase of RT to the target. In their study, they adapted vertical downward saccades. They found that backward adaptation led to a decrease of interference of the nearby distractors. They interpreted their results as the attentional field as being reduced after backward adaptation which resulted in less interference of distractors at the same distance. However, here we propose another interpretation of these results. It is possible that SA has boosted attentional performances, rather than narrowing the attention field, which would have resulted in a reduced distracting effect of the surrounding distractors. A boosting effect between attention and SA, albeit in the opposite direction, was first supported by the study of Gerardin et al. (2015) presented in the preceding section. Yet another study disclosed a coupling between SA and attention in the same direction as in Wick et al.'s (2016)s study. Indeed, Habchi and colleagues (2015) investigated the effect of SA on attentional performances. They designed a study in which they measured RT to spatially and temporally unpredictable visual targets. Subjects always kept their eye on the central fixation cross (covert attention). In their first experiment the targets could be displayed at 3°, 7°, 11° or 15° of eccentricity either in the left or in the right hemifield. The RT were measured before and after an exposure to backward SA. There were eight groups of subjects, 4 groups performed an exposure to SA and 4 other groups performed a control saccadic task. During the adaptation exposure, either VS or RS were adapted or merely performed (control), and in either the leftward or rightward direction. The authors reported that only after leftward adaptation of RS, did the RT decreased for targets presented in the left hemifield, whereas RT did not change after adaptation of rightward RS nor after adaptation of VS (whether leftward and rightward) (Figure 41, upper panels). They performed a second experiment. A single group of subjects was exposed both to backward adaptation of leftward RS and to a control task with leftward saccades in two separate sessions. In this experiment the perceptual task required subject to discriminate the hemifield of target presentation as fast as possible. The targets were presented at 3° or 7° of eccentricity either in the right or in the left hemifield. Again, the results showed that after exposure to backward adaptation of leftward RS but not after control exposure, RT were reduced for targets presented in the left hemifield only (Figure 41, lower panels). This study showed a spatially specific boosting effect of adaptation of leftward RS. However, the task did not allow to specifically investigate the attentional shift and it is not possible to determine the process that benefited from the oculomotor plasticity. **Therefore, this PhD work was dedicated to replicate these results with a finer attentional task as well as to investigate the neural substrates of the coupling they highlighted.**

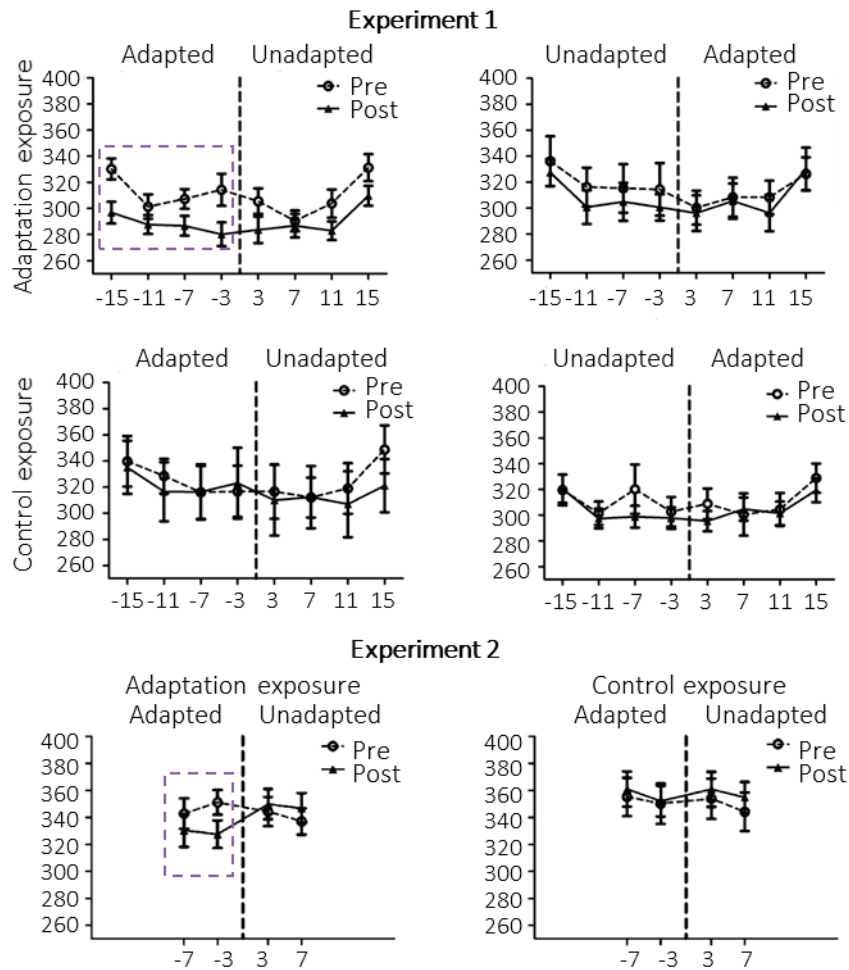


Figure 41: Reaction time results after adaptation of reactive saccades. Top 4 panels: Experiment 1 of Habchi et al. (2015). Pre- and post-exposure Reaction Times (RT) of the detection task after exposure to adaptation of leftward RS (upper left) or to control RS (lower left), and after exposure to adaptation of rightward RS (upper right) or to control RS (lower right). Bottom 2 panels: Experiment 2 of Habchi et al. (2015). Pre- and post-exposure RT of the spatial discrimination task after exposure to adaptation of leftward RS (left) or to control RS (right). The dashed purple rectangles highlight the important results, namely a decrease of RT after adaptation of leftward RS.

5. Now here we are

5.1. Hypothesis and objectives

In this brief introduction, we presented the knowledge background on which this PhD work is constructed. We first focused on the mechanisms used by human organisms to visually explore the environment. Indeed, humans are primarily relying on vision to interact adequately with the environment. We therefore introduced concepts on the visual system and how it is subtended by oculomotor behaviors, especially by the fast eye movements called saccades. Secondly, we explored the plasticity mechanisms which maintain the accuracy of the saccadic system, making this system a reliable tool for perception. Spatial attention is another mechanism that improves our perception. In the third section, we presented the endogenous and exogenous orienting systems of attention as well as the neglect syndrome as a model for understanding the role of attention in spatial cognition. Finally, we introduced the work that has been performed in the last three decades stressing out the role of the oculomotor system in spatial cognition.

As we can see, there are ties between perception and saccades, attention and spatial cognition, oculomotor plasticity and spatial cognition. My PhD work focused on highlighting that these ties are not fortuitous: they actually have functional consequences for visual perception. The literature provides evidence for a link between saccades and attention, however, the debate on the nature of this link is still ongoing. Moreover, data have accumulated in favor of the oculomotor system shaping maps of the visual space. In other words, these maps are under the control of the oculomotor plasticity especially of saccadic adaptation as saccades are the prominent oculomotor behavior. Spatial attention uses these maps to shift from one place to another in our visual environment. The main hypothesis of this PhD work is that there is a bidirectional functional coupling between visuospatial attention and oculomotor plasticity (Figure 42, upper panel). This hypothesis was supported by three main pieces of evidence in the literature: (1) SA and orienting of attention share neural substrates with a marked VS/endogenous *versus* RS/exogenous segregation: indeed both VS and endogenous attention involve the posterior IPS; whereas RS and exogenous shifts of attention both recruit the right TPJ (Gerardin et al., 2012; Corbetta et al., 2008); (2) Gerardin et al. (2015) showed that an increase in attentional load boost the SA efficiency; (3) Habchi et al. (2015) highlighted speeded RTs to targets in the left hemifield after backward adaptation of leftward RS. In addition to the main hypothesis, we posit that this coupling is modality specific, namely VS adaptation would only impact endogenous attention, and vice versa; while RS adaptation would only affect exogenous attention, and vice versa (Figure 42, lower panel). We also hypothesized that the plasticity processes are underpinned by gamma band activity on which would also rely the coupling with attention. As a first step, in the present PhD work, we only tested the impact of SA on the corresponding attention modality and neither the impact of SA on the opposite modality, nor the impact of attention on SA.

Therefore, we tested the following working hypotheses:

- Study 1: SA increases cortical excitability reflected as an increase of the power in the gamma band in the brain regions also involved in attention.
- Study 2: Reactive saccades adaptation boosts the exogenous orienting of attention.
- Study 3: Voluntary saccades adaptation boosts the endogenous orienting of attention.

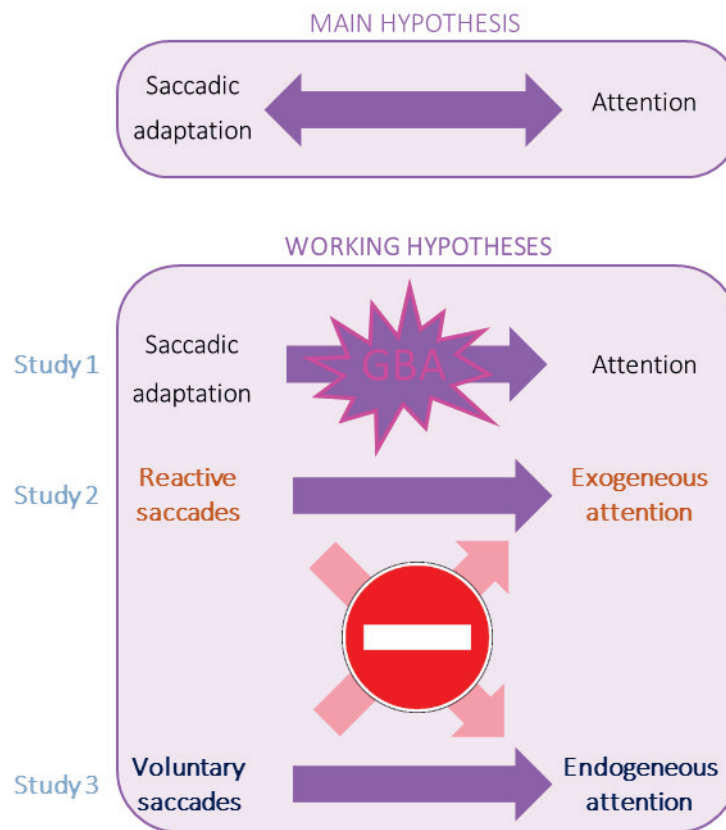


Figure 42: Hypotheses of the present PhD work. *Upper panel:* the main hypothesis predicts a bidirectional functional coupling between saccadic adaptation and attention. However, in this PhD work, we only investigated one direction of the coupling: **the impact of SA on attention**. *Lower panel:* Study 1 aimed at testing the effect of SA on the brain excitability reflected in the Gamma Band Activity (GBA). Studies 2 and 3 aimed at testing the behavioral effect of SA on attention, in the reactive/exogenous modalities and in the voluntary/endogenous modalities, respectively.

5.2. Introduction to the experimental contributions

To test the aforementioned hypotheses, we conducted three studies. They are all based on the same design: we measured attentional performances before and after an exposure to SA, and compared the pre- versus post-exposure change of performance with those of a control session in which exposure did not elicit SA, allowing us to assess the specific effects of SA on attentional performance.

In the first study, we aimed at investigating the neurophysiological basis of the coupling between SA and attention in the reactive/exogenous modality. We continuously recorded the brain magnetic fields using MEG and the eye movements using an eye tracker. The paradigm was designed to replicate behavioral results from Habchi et al.'s (2015) study which had disclosed an effect of backward adaptation of leftward RS. Attentional capture was measured with a covert speeded discrimination task. Targets were presented unpredictably in time and position and subjects were instructed to answer with their dominant hand as fast and as accurately as possible whether the target appeared to the right or left of the central fixation point. A saccadic task evaluating saccade amplitude was also performed before and after the exposure. The exposure was either adaptation or control (counterbalanced order).

In the second study, we aimed at further investigating the coupling between SA and the orienting system of attention in the reactive/exogenous modality using a specific behavioral measure of exogenous

attention orienting. The attention task was a Posner-like paradigm with peripheral cues shortly preceding the targets which had to be detected as fast as possible. Since we were interested in the benefit of attentional orienting, we only presented informative cues (100% valid) and uninformative cues. The measure of the orienting of exogenous attention was assessed as the relative change between the RT in the informative trials and in the uninformative trials (cue benefit). This attention task as well as a saccadic task were performed before and after an exposure to SA. The main objectives were both to confirm Habchi et al.'s (2015) findings for backward adaptation and to extend them to the forward direction of adaptation, our experiment thence comprised an exposure to backward adaptation of leftward RS, an exposure to forward adaptation of leftward RS, and a control exposure (mere execution of saccades).

In the third study, we investigated the effect of VS adaptation on endogenous orienting of attention. Since a possible link between VS adaptation and endogenous orienting of attention had never been studied before, our investigation concerned the backward adaptation of saccades towards the two hemifields. The attention task was a Posner-like paradigm with central cues. The SOA between the target and the cue was long enough to allow deployment of endogenous orienting. Again, the cues were either informative (100% valid) or uninformative, and the performances of attentional orienting was again assessed as the relative change of discrimination RT between the informative trials and uninformative trials. This study comprised two experiments which only differed in the eccentricity of the discrimination target. Indeed, having only one eccentricity in the endogenous task is a necessary condition to reinforce the attentional orienting. However, we were interested in two different target positions: (1) the one approximately corresponding to the endpoint of the adapted saccades and (2) the one corresponding to the size of the ISS eliciting SA. These two target positions (7.5° and 3°) were tested in two separate experiments.



1. Study 1: Effect of RS adaptation on gamma band activity

1.1. Main article



ORIGINAL ARTICLE

Saccadic Adaptation Boosts Ongoing Gamma Activity in a Subsequent Visuoattentional Task

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Abstract

Attention and saccadic adaptation (SA) are critical components of visual perception, the former enhancing sensory processing of selected objects, the latter maintaining the eye movements accuracy toward them. Recent studies propelled the hypothesis of a tight functional coupling between these mechanisms, possibly due to shared neural substrates. Here, we used magnetoencephalography to investigate for the first time the neurophysiological bases of this coupling and of SA per se. We compared visual discrimination performance of 12 healthy subjects before and after SA. Eye movements and magnetic signals were recorded continuously. Analyses focused on gamma band activity (GBA) during the pretarget period of the discrimination and the saccadic tasks. We found that GBA increases after SA. This increase was found in the right hemisphere for both postadaptation saccadic and discrimination tasks. For the latter, GBA also increased in the left hemisphere. We conclude that oculomotor plasticity involves GBA modulation within an extended neural network which persists after SA, suggesting a possible role of gamma oscillations in the coupling between SA and attention.

Key words: gamma oscillations, magnetoencephalography, oculomotor plasticity, visuospatial attention

Introduction

Humans make up to 200 000 saccadic eye movements daily. Saccades are categorized as either reactive saccades (RSs) triggered by a sudden stimulus appearance or intentionally driven voluntary saccades (VSs) (Gaymard et al. 1998). Decreased performance of saccades can impair vision (Leigh and Zee 1999). Fortunately, brain plasticity processes known as saccadic adaptation (SA) help preserve saccade accuracy by modulating oculomotor commands when neuromuscular efficacy is durably altered due to growth, aging, fatigue, or pathological conditions (PéliSSon et al. 2010).

Thanks to the double-step paradigm (McLaughlin 1967) and to modern eye-tracking techniques, SA has become a convenient tool to explore sensorimotor plasticity per se. The underlying neural

processes of SA were initially thought to be restricted to the cerebellum (Desmurget et al. 1998; Prsa and Thier 2011; Panouillères et al., 2015) but are nowadays known to comprise various cortical areas (Blurton et al. 2012; Gerardin et al. 2012).

Noteworthy, beyond an indirect effect of SA on visual perception related to plastic motoric changes, SA may also directly impact vision through modulation of visuospatial attention. Visual attention is a cognitive process that enhances the processing of visual signals arising from the attended part (“attentional focus”) of our environment with respect to unattended locations (Posner 1980; Carrasco et al. 2000). The moment-to-moment position of this focus is determined by interaction of two main orienting components: the exogenous process, directing attention

toward suddenly appearing stimuli, and the endogenous process which directs attention toward intentionally driven goals. This dichotomy between exogenous and endogenous attention echoes the one between RS and VS. The similarities between attentional and saccadic systems are such that saccades are often qualified as “overt shifts of attention” and that, in the framework of the premotor theory of attention, “covert shifts of attention” are considered equivalent to inhibited saccades (Rizzolatti et al. 1987). Although the generality of the premotor theory of attention has been criticized, its validity remains largely unaffected for exogenous attention (and corresponding RSs) (Smith and Schenk 2012). Consistent with the premotor theory of attention, neural systems controlling attention and saccades strongly overlap (Corbetta 1998). Interestingly, this overlap has also been suggested by recent studies of the cortical substrates of SA: On the one hand, adaptation of VS recruits areas of the intraparietal sulcus (IPS), whereas adaptation of RS activates the right temporoparietal junction (rTPJ) (Gerardin et al. 2012; Panouillères et al., 2014); on the other hand, IPS and rTPJ belong to the dorsal and ventral networks subtending, respectively, endogenous and exogenous attention (Corbetta et al., 2008).

Consistent with these overlapping neural substrates, a coupling between RS adaptation and exogenous attention has been proposed by the following behavioral studies. First, McFadden et al. (2002) claimed they managed to “adapt the shift of attention focus” during a covert attentional task and found that the amplitude of RS elicited just after this “adaptation” was similarly modified. Second, Gerardin et al. (2015) reported that increasing the attention load deployed during the RS adaptation exposure positively affected the amount of adaptation. Thus, these two studies suggested that experimental manipulations of the covert attention system impacts RS adaptation. Conversely, Khan et al. (2010) investigated the effect of SA on the exogenous displacement of the attentional focus which is coupled to saccades and proposed that such presaccadic shift of attention changes after SA so as to remain spatially linked to the saccadic motor vector (see also Doré-Mazars and Collins 2005). Finally, Habchi et al. (2015) disclosed the effect of adaptation of leftward RS onto covert exogenous attention, by showing after adaptation a specific increase in the processing speed of unpredictable visual stimuli in detection and spatial discrimination tasks performed without eye movement. Interestingly, this boosting effect was found not only for the target location of the adapted saccade but also for more eccentric or less eccentric targets in the adapted left hemifield. This spatial transfer can be related to the well-known fact that SA is not strictly spatially selective, as adaptation of a single saccade affects all saccades landing within an extended zone around the adapted saccade landing position, known as the adaptive field (Frens and Van Opstal 1997; Straube et al. 1997).

Here, using magnetoencephalography (MEG), we aim at determining for the first time the neural underpinnings of SA as a candidate substrate of the coupling between oculomotor plasticity and exogenous attention. We investigated Gamma power, which reflects the amplitude of the fast cortical activity (35 Hz and above) elicited by the coordinated activity of large assemblies of neurons. Given that GBA is known to predict the sensory processing efficiency (Tallon-Baudry and Bertrand 1999; Fries et al. 2001; Jensen et al. 2007) and to encode saccadic goals (Medendorp et al. 2007; Van Der Werf et al. 2008), we focused on pretarget GBA measured during the SA task as well as during a covert attention task performed pre- and postadaptation.

Materials and Methods

Subjects

The experiment adheres to the code of ethics of the World Medical Association—Declaration of Helsinki (2008) and, in agreement with French law (4 March 2002), received the approval of the Committee for Person Protection (CPP SUD EST IV, Lyon, France, A01180-39). Fifteen subjects were recorded and paid 60 euros for their participation. Among these 15, 12 subjects (7 females) were finally analyzed. The three subjects were discarded because of poor recording quality of the eye tracker (two subjects) or because of high muscular activity (one subject). The mean age of the 12 analyzed subjects was 28.3 years \pm 2.32 SD (standard deviation). Subjects were all right-handed and with a normal or corrected-to-normal vision. All subjects were free from neurological or psychiatric disorders history; cognitive disorders preventing the comprehension of the instructions; consumption of psychotropic drugs, substances, or alcohol during the last 24 h; participation to other experiments involving sensorimotor adaptation during the preceding week. After written consents obtained, each subject was assigned pseudorandomly to one of the two subgroups, corresponding to the possible orders of testing of the two experimental sessions (within-subject design, see [General Design](#) section).

Stimuli and Procedure

General Design

The experiment was carried out in the dimly lit shielded room of the MEG setup (see magnetoencephalography section). Each subject was installed in a comfortable position with the head stabilized, facing a black wood panel containing a set of red light-emitting diodes (LEDs) of 0.25° of visual angle at 114 cm from subject’s eyes, the measured contrast was 100%. Visual stimulation (LEDs ON or OFF) was controlled by a laboratory-made software running on a PC (windows XP) located outside of the shielded room. Monocular eye movements (right eye) were recorded at a 1000 Hz frequency using the EyeLink 1000 infrared tracker (SR research).

Subjects were submitted to two experimental sessions, each of which comprising identical pre-exposure and postexposure phases as well as a specific exposure phase (Fig. 1A). In the “adaptation” session, the exposure phase consisted in adaptation of leftward RSs, whereas in the “control” session, unadapted leftward RSs were performed instead. In each session, the effects of exposure on saccade and on attention were measured by comparing between the pre- and postexposure phase subjects’ performance in a test saccade task and in a visual discrimination task, respectively. Contrasting these data between the two sessions provided specific effects of unilateral SA induced in the adaptation session. The delay between the two sessions was at least 14 days in order to avoid any retention of SA between sessions, based on a previous study disclosing that the retention of adaptation observed 5 days after exposure was no longer significant 11 days after (Alahyane and Pélissier 2005).

Saccadic Tasks

The SA task, also referred to as the adaptation exposure task, implemented the double-step paradigm introduced by McLaughlin (1967). This paradigm consists in displacing the visual target while the subject is executing a saccade toward this peripheral target. Thanks to the saccadic suppression

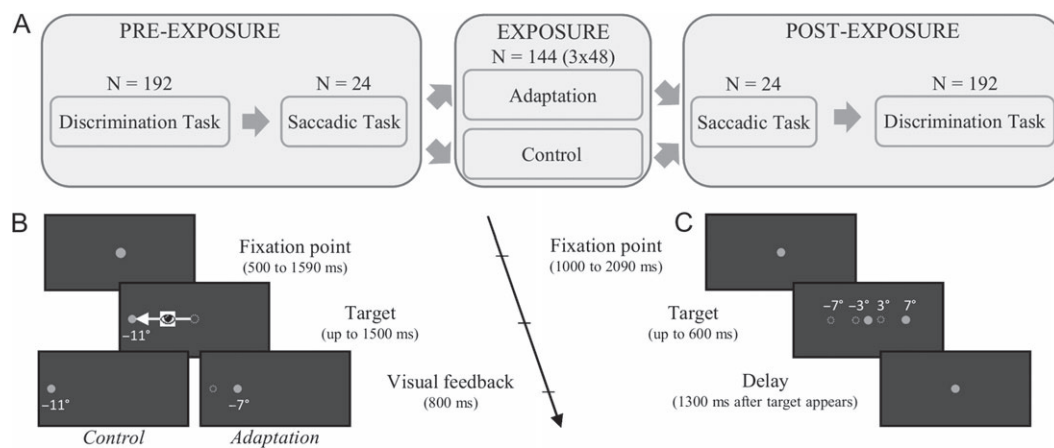


Figure 1. (A) Study general design. Each subject underwent two experimental sessions, differing only by the Exposure phase (either Adaptation or Control). N = number of trials. (B) Timeline of a trial in the exposure task. Note that in the pre- and postexposure tasks (not shown), visual feedback is suppressed (visual scene is turned off) as soon as the saccade is detected. (C) Timeline of a trial in the discrimination task. The dotted points represent the potential target position (red in the experiment), only one is turned on in each trial (at 7° in this example).

phenomenon, this intrasaccadic visual displacement is usually not consciously perceived by subjects and leads to a mismatch between postsaccadic eye fixation and target location which is interpreted by the central nervous system as a saccade aiming error. This procedure yields a progressive, exponential-like, change of saccade gain reaching an asymptote after around 100 trials in humans (see for review, Hopp and Fuchs 2004; Pélisson et al., 2010), thus, we chose a total number of 144 adaptation trials to optimize the steady state level of adaptation and the level of after-effect.

Sequence of events in an adaptation exposure trial (Fig. 1B). Subjects had first to fixate a central LED. After a delay of 500–1590 ms (uniformly randomized), a peripheral LED was flashed along the horizontal meridian at an eccentricity of 11° of visual angle to the left (-11°) of fixation and simultaneously, the central LED was turned off. The subject had to make a saccade toward the peripheral target (maximum allocated time: 1500 ms). When the saccade was detected (online eye velocity threshold: $80^\circ/\text{s}$), the visual target was shifted 4° inward, namely, an LED at -7° of visual eccentricity was turned on, while the LED at -11° was turned off. This new visual target remained visible for 800 ms after the detection of the saccade to provide visual feedback about the target location and allow corrective saccades. The subject then had a delay of 2000 ms to blink and look back to the central fixation dot before the next trial started.

The saccadic control task, also referred to as the control exposure task, was identical to the adaptation task except that there was no jump of the visual target in any of the trials, the -11° LED staying on for 800 ms after the detection of the saccade.

For both adaptation and control exposure, the task comprised 144 trials, presented in 3 blocks of 48 trials, respectively, referred to as exposure 1, exposure 2 and exposure 3. Between each block, subjects were allowed a 10–30s rest.

The pre- and postexposure saccadic tasks were identical to the exposure tasks except that in this case, the visual target could appear in either hemifield and was turned off at the detection of the saccade (no visual feedback). Each pre- and postexposure tasks consisted in one block of 24 trials (12 for each side, randomly presented). Comparison between pre- and postexposure saccadic tasks allowed the determination of the adaptation after-effect (relative change of saccade amplitude in postexposure vs. pre-exposure) and thus quantitative assessment of the SA behavioral efficiency.

Discrimination Task

The exogenous attentional task (Fig. 1C) was performed before and after the exposure tasks (referred to as pre-exposure discrimination and postexposure discrimination, respectively) and consisted in 4 blocks of 48 trials (192 in total). Subjects had to fixate a central LED which remained continuously on. A peripheral LED was flashed after a delay from 1000 to 2090 ms (uniformly randomized) at a randomly selected position among 4 possible locations (equal probability: 12 repetitions each) either in the left hemifield (-7° or -3° of eccentricity) or in the right hemifield (3° or 7° of eccentricity). Subjects were instructed to discriminate as fast as possible the hemifield of the target by using a two-button box in their right hand: They had to push the left button with their index for a left target and the right button with their middle finger for a right target. The two-button box was in the subjects' right body space. The target LED turned off as soon as the answer was provided or after a limiting time of 600 ms. The trial ended 1300 ms after the target onset. Between each block, subjects were allowed a 10–30s rest. The end of the entire task was signaled by the extinction of all LEDs. Trials in which a blink occurred within a 500ms period before the target onset were aborted. Subjects were told to blink just after providing their answer.

Behavioral Data Analyses

Saccadic Tasks

Preprocessing. The eye movement data were analyzed off-line using custom software developed in Matlab (MathWorks Inc.). The beginning and end of each saccade were identified based on a velocity threshold of $30^\circ/\text{s}$. Saccadic amplitude was the difference between eye positions measured 50 ms before saccade onset detection and 50 ms after saccade offset detection. The gain was computed as the ratio of the saccadic amplitude and target retinal eccentricity (difference between target position and starting position of the saccade). The saccadic peak velocity was also extracted and divided by the amplitude of the saccade to obtain a normalized peak velocity. For the pre-exposure, the exposure, and the postexposure saccadic tasks, trials, in which the saccadic gain was less than 0.5 or outside the range of ± 3 SD from the subject's mean gain computed in the same phase and hemifield, were discarded from further analysis. Trials with a

blink or an anticipated saccade (falling within the -1000 ms pretarget to 100 ms post-target period) were also discarded, leaving on average 23.4 trials ± 1.3 (SD by subject) per saccadic task (24 in total) and 135.4 trials ± 6.5 (SD by subject) per exposure task (144 in total). The repartition of saccadic valid trials (after rejection of invalid saccades) was tested using a repeated-measures ANOVA (rmANOVA) with the side of the target appearance (left or right), the phase (pre- or postexposure), and the session (adaptation or control) as within-factors. No main effect of target side on the amount of valid trials was found ($F(1,11) = 47.8$; $P = 0.50$) nor any interaction between the side and the other factors (side \times phase: $F(1,11) = 34.4$; $P = 0.57$; side \times exposure: $F(1,11) = 1.32$; $P = 0.27$; side \times phase \times exposure: $F(1,11) = 9.371668 \cdot 10^{-28}$, $P = 1$). Finally, to check for the repartition of valid trials in the exposure task, we performed the rmANOVA with the factor exposure (adaptation or control). Again, no main effect of the exposure was highlighted ($F(1,11) = 9231$; $P = 0.78$).

Statistical Analysis. Since SA was critical to our hypothesis, we needed to ensure that subjects showed a significant decrease in saccade gain only after the adaptation exposure in the adapted left hemifield. Thus, for each individual, we performed a unilateral Student's *t*-test comparing the saccade gain between the pre- and the postexposure phases, separately for each exposure and for each hemifield of target appearance. The resulting 48 *P*-values were corrected for multiple comparison using the false discovery rate (FDR; Benjamini and Hochberg 1995) correction.

We computed the percentage of gain change achieved in each block relative to the final gain change (measured in exposure block 3), and then compared these percentage values between exposure 1 and 2 and between exposure 1 and 3 using an unilateral student test corrected using the FDR correction.

Finally, to rule out the hypothesis that SA exposure could result in a period of arousal, we used the peak velocity as a marker of arousal (Di Stasi et al. 2013). Therefore, we computed for each subject, each exposure, each phase, the mean normalized peak velocity. We performed the rmANOVA on normalized peak velocity (dependent variable) with the phase (pre- or postexposure) and the exposure condition (adaptation or control) as within-subjects factors.

Discrimination Task

Preprocessing. Data of the discrimination phase were analyzed with the open-source software R (The R Core Team, 2013). Only trials with a correct response were considered. Trials with a reaction time (RT) outside the 200 – 600 ms time window after target onset or exceeding ± 3 SD from the subject's mean were also excluded, leaving on average 174.3 trials ± 4.85 (SD by subject) per task (192 in total). The repartition of the amount of valid trials (dependent variable) was tested using the rmANOVA with the side of the target appearance (left or right), the phase (pre- and postexposure) and the session (adaptation or control) as within-factors. We found only a significant side effect ($F(1,11) = 6.31$; $P = 0.03$) consistent with the frequently observed hemifield imbalance of visuo-motor performance, but importantly for our behavioral analysis there was no interaction between the side and the other factors (side \times phase: $F(1,11) = 0.20$; $P = 0.66$; side \times exposure: $F(1,11) = 0.65$; $P = 0.44$; side \times phase \times exposure: $F(1,11) = 0.52$; $P = 0.48$).

Statistical Analysis of RTs. The rmANOVA was performed on median RTs (dependent variable) with the side of the target appearance (left or right), the phase (pre- or postexposure) and

the session (adaptation or control) as within-factors. Paired Student's *t*-tests were used as post hoc analysis on the main effects revealed by the rmANOVA. Power analysis was performed through the G*Power software (Faul et al. 2007) with a total sample of 12 , one group (within design), 16 repetitions, correlation among subjects of 0.5 , and ϵ coefficient for nonsphericity correction of 0.36 for the target position factor in the discrimination task.

Magnetoencephalography

Data Acquisition

The MEG data were acquired with a 275 -sensor axial gradiometer system (CTF Systems Inc.) with a continuous sampling rate of 600 Hz, a 0 – 150 Hz filter bandwidth, and first-order spatial gradient noise cancellation.

Head position relative to the gradiometer array was acquired continuously using coils positioned at three fiducial points: nasion, left and right preauricular points. Head position was checked before each block to ensure that head movements did not exceed 1 cm in comparison to the first block.

Anatomical head/brain images (either available beforehand or obtained using a 3 T Siemens Magnetom whole-body scanner) were used for reconstruction of individual head shapes to create forward models for the source reconstruction procedures. The coregistration of the fiducial points was carried out using CTF's software (CTF Systems Inc.).

Preprocessing and Trials Rejection

Electrophysiological analyses concerned data collected during the pre- and postexposure discrimination and saccadic tasks, as well as during the exposure blocks 1, 2, and 3. The aim of the study was to investigate lasting effects of SA on neuronal excitability by isolating persistent changes of GBA across trials. Therefore, we avoided the time windows during which other types of processing—such as the computation of postsaccadic error—could happen, and electrophysiological analyses were hence focused on the pretarget period in all the tasks.

First of all, trials already excluded at the behavioral preprocessing step were discarded from the electrophysiological analyses. Trials with head movements exceeding 1 cm (up to 1.3 cm for two subjects) were also discarded, as well as trials with a blink occurring in the 1000 ms period preceding presentation of the peripheral target. Data segments contaminated with muscular activity or sensor jumps were excluded semimanually with a threshold of 2500 and $10\,000$ femto-Tesla, respectively, using the ELAN software package for electrophysiological analysis (<http://elan.lyon.inserm.fr/>; Aguera et al. 2011). In total, 20 trials ± 3 (SD) in the saccade tasks, 34.8 trials ± 8.3 in each block of the exposure task and 163.7 trials ± 12.4 in the discrimination tasks remained for the analysis. The amount of valid trials was not significantly different between adaptation and control conditions, neither in the saccade tasks ($\chi^2(33) = 11.6$, $P = 0.99$) nor in the exposure task ($\chi^2(55) = 64.4$, $P = 0.18$) and nor in the discrimination tasks ($\chi^2(33) = 25.4$, $P = 0.83$). Data were filtered with a high-pass filter at 0.01 Hz and with band-stop filters between 47 – 53 , 97 – 103 , and 147 – 150 Hz. MEG data preprocessing and analyses were carried out using functions supplied by the fieldtrip toolbox (REF; <http://www.ru.nl/neuroimaging/fieldtrip>; Oostenveld et al. 2011).

Sensor-Level Analyses

Time–frequency (TF) representations were calculated using Morlet wavelet decomposition with a width of four cycles per

wavelet ($m = 7$) at center frequencies between 30 and 150 Hz, in steps of 1 Hz and 10 ms, and averaged across all trials of each condition (phases of discrimination task, phases of saccadic task, blocks of exposure task, and type of session: adaptation or control). Data extracted in the pre-exposure saccadic task were used as baseline data for the analyses of exposure 1, 2 and 3, as well as of the postexposure saccadic task, whereas data in the pre-exposure discrimination task were used as baseline for the analysis of the postexposure discrimination task; in all cases, baseline time window was defined as the 900–100ms pretarget period to prevent any contamination of the baseline signal by blink- or target-related activity:

$$\text{Baseline}_{\text{Saccade}} = \text{mean}(\text{Gamma power}_{\text{Saccade PRE}[-900; -100]})$$

$$\text{Baseline}_{\text{Exposure}} = \text{mean}(\text{Gamma power}_{\text{Saccade PRE}[-900; -100]})$$

$$\begin{aligned} \text{Baseline}_{\text{Discrimination}} \\ = \text{mean}(\text{Gamma power}_{\text{Discrimination PRE}[-900; -100]}) \end{aligned}$$

Then we computed for each task of interest the change of gamma power relative to baseline, by dividing each TF point of each sensor by the corresponding mean baseline activity, according to the following expression:

$$\begin{aligned} \% \text{Adaptation or } \% \text{Control}_{\text{task of interest}} \\ = \frac{\text{Gamma power}_{\text{task of interest}} - \text{Baseline}}{\text{Baseline}} \end{aligned}$$

The data were smoothed in the time domain (50 ms) and in the frequency domain (5 Hz). The sensor-level analysis performed on every TF points allowed us to decipher the frequencies and time windows for which the SA effect was the strongest. Then, we computed the difference between “% Adaptation” and “% Control”. For the statistical contrast, this difference was compared with zero using a nonparametric cluster-based permutation (CBP) analysis (Maris and Oostenveld 2007). This test first calculates paired t-tests between % Adaptation and % Control for each sensor at each TF points, which are then thresholded at a chosen P -value which sets the conservativeness of the test (reported as “cluster threshold”). We decided to set the cluster threshold to be as conservative as possible while obtaining comparable cluster size among the different tasks. Significant clusters are defined as sets of adjacent sensors showing a continuum of significant TF points. Subsequently, the procedure is repeated 1000 times on shuffled data in which the condition assignment (% Adaptation and % Control) within each individual is permuted randomly. On each permutation, the maximum t -value is retained, yielding a distribution of 1000 t -values. Finally, this distribution is used as a reference to determine whether the t -value of each cluster, as calculated on the real assignment of the conditions, is likely to come from the same probability distribution (P -value > 0.05) or rather differs significantly from this random perturbation probability distribution (P -value < 0.05).

The Pre- and Postexposure Saccadic Task. To determine the effect of SA on GBA, we computed the change of the GBA during the postexposure saccadic task relative to baseline for the adaptation and control sessions (% Adaptation_{Saccade} and % Control_{Saccade}, as defined above). The difference between these values was then compared with zero with the same CBP analysis as described above, allowing to assess the specific impact of SA on GBA. As neutral outcome criterion, we used the

same procedure to compare the raw GBA of the pre-exposure saccadic phase between the adaptation and the control sessions.

The Saccadic Exposure Task. We proceeded identically for the exposure task, considering the three exposure blocks separately. The change of the GBA relative to the baseline was computed in exposure 1, 2 and 3 separately for the adaptation session (e.g., % Adaptation_{Exposure 1}) and for the control session (e.g., % Control_{Exposure 1}). For each exposure block, the difference between these values was then compared with zero with a CBP analysis, allowing to assess the specific impact of SA on GBA during each block of the exposure.

The Discrimination Task. We computed the change of GBA in postexposure discrimination relative to baseline, separately for the adaptation session (% Adaptation_{Discrimination}) and for the control session (% Control_{Discrimination}). Again, the specific impact of SA was extracted by comparing the difference of the two relative changes to zero through a CBP analysis. As neutral outcome criterion, we used the same procedure to compare the raw GBA of the pre-exposure discrimination of the adaptation and the control session.

Since our initial hypothesis was interested in the effect of SA on an attentional task, the CBP used to analyze the discrimination task implemented a two-tailed paired Student’s t -test. This revealed significant positive modulations (see Sensor-Level Analyses in Results section) which led us to look for positive modulations in the other tasks, using one-tailed tests.

In summary, we derived five main contrasts of interest, each of which being then submitted to a CBP analysis. We performed the permutations over a 800ms period of interest, from 900 ms to 100 ms pretarget. The frequency range was set from 50 to 100 Hz.

$$\text{Saccade contrast: } \% \text{Adaptation}_{\text{Saccade}} \text{ vs } \% \text{Control}_{\text{Saccade}}$$

Exposure contrasts:

$$\% \text{Adaptation}_{\text{Exposure 1,2 or 3}} \text{ vs } \% \text{Control}_{\text{Exposure 1,2 or 3}}$$

Discrimination contrast:

$$\% \text{Adaptation}_{\text{Discrimination}} \text{ vs } \% \text{Control}_{\text{Discrimination}}$$

Source-Level Analyses

These analyses aimed at estimating the candidate brain regions driving the modulation of GBA disclosed by the sensor-level CBP analysis (see Sensor-Level Analyses in Results section). In these TF windows, we have used the frequency-domain-adaptive spatial technique of dynamical imaging of coherent sources (Gross et al. 2001). First, data from the two entire sessions were concatenated, and cross-spectral density (CSD) matrix (from -900 to -100 ms relative to target onset, lambda 15%) were calculated using the multitaper method with a target frequency of $75 \text{ Hz} \pm 25$. For each subject, an anatomically realistic single-shell head model was generated based on individual head shapes (Nolte 2003). A grid with 0.5 cm resolution was normalized on an MNI template and then morphed into the brain volume of each subject. Leadfields for all grid points along with the CSD matrix were used to compute a common spatial filter allowing to estimate the spatial distribution of power for all TF windows of interest. Based on the most pronounced significant differences found at the sensor level and the observation of the data, we decided to choose for all

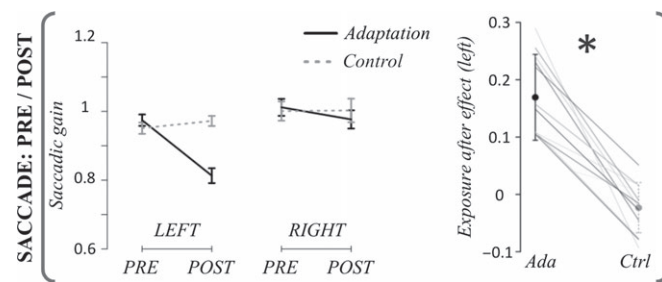


Figure 2. Pre- and postexposure saccadic tasks showing the efficiency of the leftward SA. **Left:** Group mean (\pm SEM) of saccadic gain. **Right:** Individual data of percent gain change between the pre- and the postexposure tasks. Solid black and dotted gray stand for group mean (\pm SD) of the adaptation and the control exposure, respectively. Gray lines stand for individual values.

saccadic tasks (pre- and postexposure, and the three exposure blocks) an a priori time window of 300 ms starting at -400 ms before target onset. Following the same types of observation of the data, time windows of both discrimination pre-exposure (used as baseline) and discrimination postexposure were selected as 90–100 ms pretarget. The frequency bands were chosen to encompass the most pronounced differences observed at the sensor level across all tasks, leading to a common frequency band of 75 ± 25 Hz.

Then, following the same rationale as for the sensor-level analyses, the GBA differences between % Adaptation and % Control were computed and tested against zero using a CBP analysis.

Results

Behavioral Analyses

Pre- and Postexposure Saccadic Tasks

The mean saccadic gain in pre- and postexposure, as well as the individual and mean adaptation after-effect, is illustrated in Figure 2. Eleven subjects showed in the adaptation session a significant decrease in the saccadic gain for target presented in the left hemifield in the postexposure as compared with the pre-exposure, with corrected P -values <0.05 (type I error threshold), the 12th subject had an effect approaching significance with a P -value of 0.053. The twelve results all achieved a power larger than 98% and a large effect size (>0.9), we thus considered that all subjects demonstrated a significant after-effect due to SA. Moreover, no significant modulation of saccadic gain was highlighted, neither for responses toward both hemifields in the control session nor for responses toward the right hemifield (unadapted) in the adaptation session.

Regarding the normalized peak velocity, we found no effect of the exposure ($F(1,11) = 2.03$; $P = 0.18$), nor an effect of the phase ($F(1,11) = 0.26$; $P = 0.62$), and nor an interaction between the exposure condition and the phase ($F(1,11) = 1.17$; $P = 0.3$).

Exposure Saccadic Task

As shown in Figure 3, most of the saccadic gain change reached at the end of adaptation exposure was achieved during exposure 1 (on average $47.9 \pm 25\%$), then during exposure 2 ($33.4 \pm 16.9\%$) and exposure 3 ($18.6 \pm 19.9\%$). The difference between the percentage of adaptation achieved during exposure 1 and exposure 2 is not significant ($t_{(11)} = 1.33$; $P = 0.11$). The percentage achieved in exposure 1 is significantly larger than that achieved in exposure 3 (Cohen's $d = 1.28$; $t_{(11)} = 2.42$; $P = 0.017$; corrected to 0.034 with the FDR correction; achieved power = 0.97).

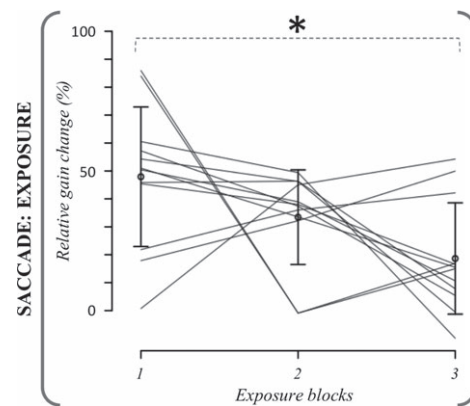


Figure 3. Percentage of SA during exposure. Percent gain change (relative to total gain change reached at exposure 3) for each exposure block: individual data and group mean are plotted as black lines and black points (\pm SD), respectively.

Discrimination Task

The performance in the discrimination task was evaluated by computing the median RT of subjects' discrimination responses. The rmANOVA revealed a significant main effect of phase (pre-exposure vs. postexposure, partial $\eta^2 = 0.49$; $F(1,11) = 10.6$; $P = 0.008$; achieved power = 0.99). As shown in Figure 4, post hoc unilateral paired Student's t -tests indicated that subjects were faster after the exposure task (either adaptation or control) in comparison to before exposure ($t_{(11)} = 3.19$; $P = 0.009$). However, this phase effect did not significantly interact with the type of exposure, nor with the target hemifield. This indicates that the tendency which can be seen in Figure 4 (compare left and right panels) does not reach significance, contrary to our predictions. In conclusion, these behavioral data disclosed a general improvement of performance after exposure, but no specific effect of adaptation on discrimination performance could be statistically established.

Sensor-Level Analyses

Neutral Outcome Criteria

We first verified that the GBA used as baseline in our analyses presented below did not differ significantly between, on the one hand, the pre-exposure saccadic task of the adaptation and the control session and, on the other hand, the pre-exposure discrimination task of the adaptation and the control session. None of these tests did disclose any significant result, allowing us to use these periods to compute baseline GBA.

Pre- and Postexposure Saccadic Tasks

Testing for the saccadic tasks contrast, the CBP test revealed a trend to significance of the difference between the two exposure types. This trend was most pronounced from -400 ms to -100 ms and from 50 to 100 Hz over two localizations: One on a broad right area of sensors and the second on a left posterior area, with a cluster threshold of 0.05 and P-value of 0.09 (Fig. 5 Top panels).

Exposure Task

Using the CBP test separately for the three exposure blocks as defined in Methods revealed no significant difference between the adaptation and the control sessions for any of these contrasts (exposure 1, exposure 2 or exposure 3) at the sensor level.

Discrimination Task

Testing for the discrimination contrast, the CBP test revealed a significant difference between the two exposure types. This difference was most pronounced over two localizations: One on the right anterior sensors and the second on the left posterior area (Fig. 5 Bottom Panels). The difference was sustained in time (during the entire period of interest from -900 to -100 msec) at both localizations and was from 70 to 100 Hz for the

right anterior sensors and from 60 to 90 Hz for the left posterior sensors. The cluster threshold was 0.005 and a P-value of 0.001.

To summarize, we found differences of GBA between adaptation and control conditions that tended to or was highly significant, respectively, for the saccade and discrimination contrasts. Note that in left hemisphere, the clusters overlap between the two tasks, and in the right hemisphere some overlap is also observed.

Source-Level Analyses

After selecting the time and frequencies of interest from the CBP analysis at the sensor level (see Sensor-Level Analyses in Results section), the CBP tests revealed a difference of GBA modulation between adaptation and control conditions, as detailed in the following. The cortical regions highlighting more than 10 significant voxels are listed in Table 1 for both the pre- and post-exposure saccadic (referred as “Saccade”) tasks and the discrimination task (referred as “Discrimination”).

Pre- and Postexposure Saccadic Tasks

We found a difference with a cluster threshold of 0.02 and a P-value of 0.056 (Fig. 6 upper left panel). Although this P-value did not reach the classical statistical threshold, it is very close

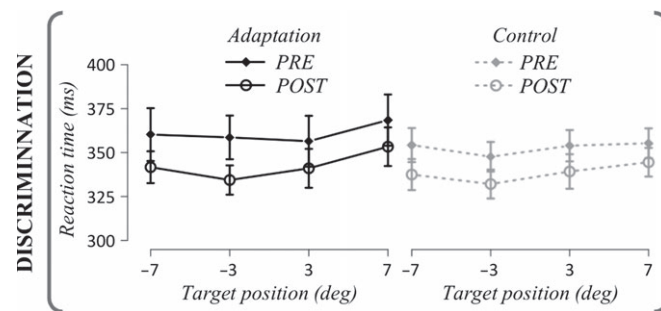


Figure 4. Pre- and postexposure behavioral results of the RTs in the discrimination task. Group mean (\pm SEM) of median RTs (ms) in the adaptation session (left panel) and in the control session (right panel). A general decrease between the pre- and the postexposure phases is observed but is not specific to the exposure conditions.

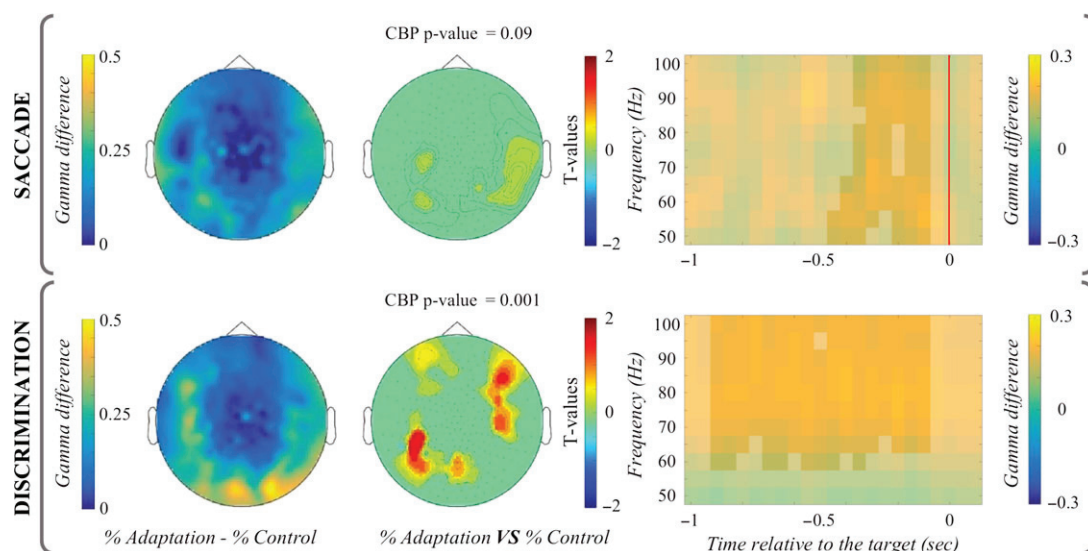


Figure 5. Gamma difference between adaptation and control evidencing the specific increasing effect of the exposure to SA. Left: Topographies of group grand average power (60–90 Hz) from -900 ms to -100 ms. Middle: t-values’ topographies of the CBP analysis masked at $P = 0.1$ for the saccade task and at $P = 0.05$ for the discrimination task. Right: TF plots of the average power of the gamma difference across significant clusters.

Table 1 Cortical and subcortical regions found from the CBP analysis at the source level

Region	Left hemisphere	Right hemisphere
Angular	Discrimination	
Calcarine	Saccade	
Caudate	Discrimination	Discrimination
Cingulum	Discrimination	
Fusiform		Saccade/Discrimination
Heschl		Saccade
Hippocampus		Saccade/Discrimination
Insula	Discrimination	Saccade
Lingual	Saccade	
Occipital inferior		Saccade
Occipital middle	Saccade	Saccade
Parahippocampal		Saccade/Discrimination
Paracentral lobule	Discrimination	Discrimination
Parietal inferior	Discrimination	Saccade/Discrimination
Parietal superior		Discrimination
Postcentral		Saccade/Discrimination
Precentral		Saccade/Discrimination
Precuneus		Discrimination
Putamen		Saccade
Rolandic operculum		Saccade/Discrimination
Supramarginal		Saccade
Temporal inferior		Saccade
Temporal middle		Saccade
Temporal superior		Saccade
Thalamus	Discrimination	Saccade /Discrimination

to significance and we consider this result as noteworthy because 1) the small number of trials in this task likely contributed to this failure to reach significance (maybe explaining also the large size of the cluster), 2) a similar pattern of GBA increase in the discrimination phase clearly reached statistical significance (P -value = 0.001) with only one additional subject showing the effect (Fig. 6 lower right panel: 11 subjects) as compared with the 10 subjects for the discussed GBA change in the adaptation phase (Fig. 6 upper right panel), 3) a significant correlation was found between the SA gain change and the GBA activity during adaptation exposure in the right parietal cortex (Supplementary Results).

Discrimination Task

For the discrimination contrast, we found a significant difference with a cluster threshold of 0.008 and a P -value of 0.001 (Fig. 6, lower left panel).

Discussion

GBA has been previously shown to increase in relation to various perceptual, motor, and cognitive processes (see Introduction). Here, we questioned the link between GBA and these processes combined together, thanks to a design testing the effect of oculomotor plasticity on exogenous attention. Furthermore, this study is the first to report whole-brain electrophysiological signal changes in relation to SA. Based on within-subjects comparisons between SA and control exposures, our results highlighted a sustained SA-specific increase of the GBA. More precisely, during the postexposure saccadic task, a trend of GBA increase was disclosed in widespread areas of the right hemisphere including the inferior parietal lobe, the superior temporal lobe, the supramarginal gyrus region, the

insula, and the sensorimotor cortex (Table 1). In addition, during the postexposure attentional task, a strong GBA increase was found in both hemispheres.

One major finding is that GBA can be entrained by SA, a well-established model of sensorimotor plasticity. SA requires a continuous change in the brain's functional architecture to encode the new relationship binding the sensory vector, representing the position of the target from the current gaze position, and the motor vector sent to the extraocular muscles to accurately shift gaze position toward this target. The parietal cortex and the supramarginal regions at the temporoparietal junction were found to be modulated by SA. These findings provide further support for an involvement of the parietal cortex and of the temporoparietal junction in SA, complementing previous fMRI and TMS data in humans (Gerardin et al. 2012; Panouillères et al. 2014; Pélişson et al. 2018). They are also consistent with recent electrophysiological recordings in monkey lateral intraparietal area (LIP) (Zhou et al. 2016). As will be detailed below, we suggest that the increase in GBA that we disclose in the cerebral cortex is a signature of the error processing subtended by the cerebellum. Note however that an additional involvement of GBA directly underlying the plastic change of saccadic commands during SA cannot be excluded. In addition, as the other neurophysiological studies of SA in humans or monkey have neglected the cerebral cortex and rather focused on the brainstem–cerebellum circuits (see for reviews, Iwamoto and Kaku 2010; Pélişson et al. 2010; Prsa and Thier 2011), the available evidence in the literature is too limited to allow us to fully understand the large extent of the cortical and subcortical networks where we found an increase in GBA. Nevertheless, regarding the parietal cortex, the SA-induced GBA increase could correspond to a more general role in motor plasticity, as gamma activity during hand movement execution has been shown to be enhanced after visuomanual learning, in sensors above the right parietal lobe (Perfetti et al. 2011). The involvement of GBA in numerous forms of functional plasticity is supported by its proposed link with cellular plasticity mechanisms. Actually, GBA represents a precise temporal framework for synaptic plasticity in terms of gain modulation of synaptic weight (Traub et al. 1998; Bosman et al. 2014). We thus propose that the GBA increase in the regions at the crossroad of somatosensory, temporal, and parietal cortices reported here subtends the updating of visuomotor maps. Such SA-related updating of visuomotor maps has been predicted based on behavioral data of adaptation transfer to visually guided motor tasks and to visual localization tasks (reviewed by Zimmermann and Lappe 2016). The information for the updating could be provided via the cerebello–thalamo–cortical pathway, as the cerebellum is suggested by the literature to compute an error signal between the predicted and actual motor consequences (Peterburs and Desmond 2016).

The involvement of the parietal cortex, conjunctly with the cerebellum, in visuomotor plasticity has also been studied thanks to the prismatic adaptation (PA) paradigm. In this case, sensorimotor adaptation of arm reaching movement is induced thanks to a visual shift elicited by prismatic goggles. In the model proposed by Pisella et al. (2005), the progressive modification of the arm movement is thought to rely on cerebello–cortical interactions, whereby the cerebellum inhibits the posterior parietal cortex (PPC), a cortical involvement which could account for the known effects of PA on spatial cognition (Striemer and Danckert 2007; Jacquin-Courtois et al. 2013; Reed and Dassonville 2014). Although much less investigated than PA, SA might also involve cerebello–thalamo–cortical interactions.

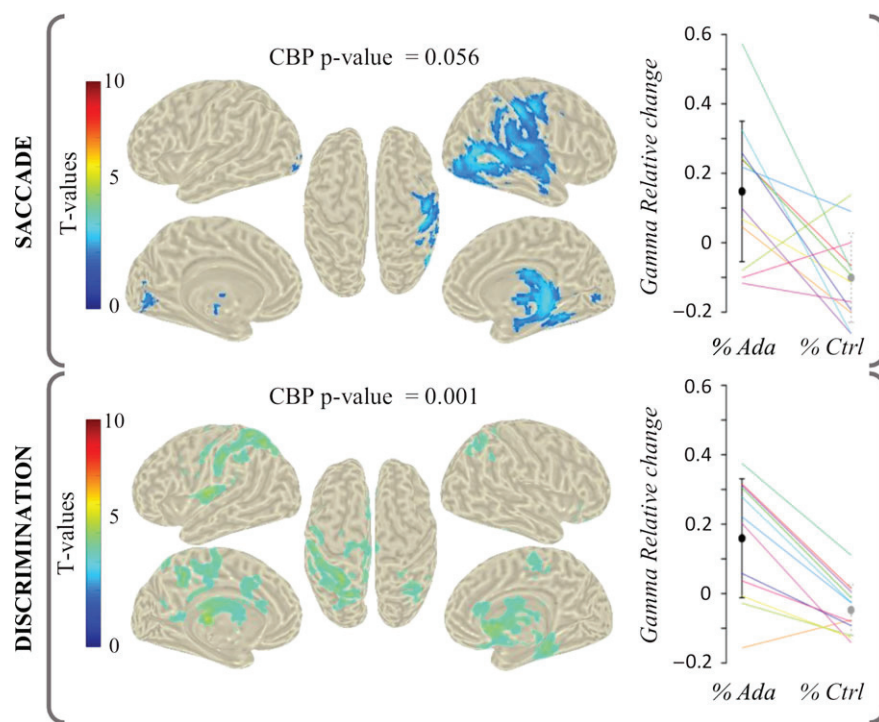


Figure 6. Source reconstruction of the positive gamma power increase in the saccadic task (top) and the discrimination task (bottom). Left: t-values' distributions of the adaptation versus control contrast, masked at $P = 0.05$ (masked at $P = 0.057$ for the saccade contrast), are displayed on surface cortical maps. Right: Average gamma power (\pm SD) change across significant voxels for the adaptation session (solid black) and for the control session (dotted gray). Individual data are represented by colored lines.

Indeed, SA heavily relies on the cerebellum (e.g., Desmurget et al. 1998; Straube et al. 2001; Golla et al. 2007; Prsa and Thier 2011; Panouillères et al., 2012; Panouillères et al., 2015). Moreover, Prevosto et al. (2010) reported that, in monkeys, the cerebellum projects via the thalamus to the parietal cortex and especially to the LIP, known to be involved in eye movement and visuospatial attention (Colby et al. 1995). In addition, clinical observations suggest that SA involves the cerebello–thalamo–cortical pathway (Gaymard et al. 2001; Zimmermann et al. 2015). Finally, SA affects visual cognition (Hernandez et al. 2008; Cotti et al. 2009; Khan et al. 2010; Zimmerman and Lappe 2010; Habchi et al. 2015) and involves the parietal and temporoparietal cortices (Gerardin et al. 2012; Panouillères et al. 2014). The present results support this hypothesis of cerebello–cortical interactions subtending SA and further suggest that the updating of spatial representations in the parietal cortex following SA is mediated through GBA changes.

The currently reported involvement of the temporal cortex and of the sensorimotor cortex was less expected. However, note that the contribution of motion sensitive areas of the temporal cortex (MT/V5) is consistent with the fMRI finding of an activation related to the adaptation of RSs (Gerardin et al. 2012). Concerning the sensorimotor cortex, an intriguing hypothesis is that, although extraocular proprioceptive afferents seem not necessary for SA in the monkey (Lewis et al. 2001), SA modifies the eye position sense derived from extraocular proprioception. Indeed, studies in the monkey and in humans have suggested that eye proprioceptive signals are processed bilaterally in an area of the sensorimotor cortex (Wang et al. 2007; Balslev et al. 2011). What are the relative weights of proprioceptive and of efference copy signals in the SA-related changes of eye position sense and to what extent their cortical neural substrates overlap remain to be determined.

Finally, the involvement of the insula in the right hemisphere during the postexposure saccadic task and in the left hemisphere during the postexposure discrimination task echoes a fMRI study (Blurton et al. 2012) which reported a bilateral activation of the insula during SA. These authors suggested that such insula activation disclosed by contrasting the SA exposure phase to the pre-exposure phase was related to saccade inaccuracy.

The initial objective of the present study was to decipher the neural substrates of the coupling between adaptation of RSs and orientation of exogenous attention. Such coupling is supported by converging evidence (McFadden et al. 2002; Khan et al. 2010; Gerardin et al. 2015; Habchi et al. 2015). Unfortunately, although using an identical design to Habchi et al.'s (2015), we failed to reproduce their finding of a significant decrease in discrimination RTs specifically after adaptation of leftward RSs. Note however that these two experiments differ in the stimuli used: The contrast of their targets (gray circles presented on the gray background of a computer screen) was 50%, whereas in the present study, due to MEG environment constraints, targets (red LEDs on a black background) reached a contrast of 100%. Given that attention increases the sensitivity to contrast (Carrasco et al. 2000), we interpret our negative finding as related to the too high contrast of our stimuli which did not provide optimal condition for attentional performances to be boosted by SA. The unspecific decrease in RT after both adaptation and control exposures suggests a learning effect between pre- and postexposure, possibly further masking any residual effect of SA on attention. Nonetheless, it is still possible that some specific effect of SA on attention can be reflected in the neural dynamics. Indeed, previous studies of PA reported significant changes of metabolic or electrophysiological

markers of cognitive functions without any behavioral evidence (Crottaz-Herbette et al. 2014; Martin-Arevalo et al. 2016). The large extent of the network showing a specific GBA increase after SA could suggest that the latter led to an increase in arousal. However, we found no evidence for an increase after SA of saccade peak velocity, as a sensitive marker of arousal (Di Stasi et al. 2013). Thus, changes of arousal are unlikely to account for the observed GBA modulations.

Furthermore, GBA increased preferentially in the left hemisphere and in sensorimotor areas, during the subsequent discrimination task. Two explanations can be provided for this lateralization in the left hemisphere: Either it resulted from the displacement of the source of GBA increase present in the right hemisphere during adaptation exposure or was already present during the SA exposure but could not be established statistically. In the frame of this latter alternative, we suggest that this activity (ipsilateral to the saccade) is related to the SA-inducing, intrasaccadic target jump toward the right hemifield, providing a rightward bias of the saccade aiming error. The resurgence of the GBA in the subsequent discrimination task could be the result of a retention of such a rightward bias introduced progressively during the adaptation procedure. We further suggest that this activity could account for the distortion of space demonstrated by previous behavioral studies. Indeed, Zimmermann and Lappe (2009) showed that SA induces a shift of the perceived localization of objects flashed before the saccade, and Zimmerman and Lappe (2010) demonstrated that this SA-related visual mislocalization occurs even when saccades were not executed, suggesting that spatial visual representations are shaped by oculomotor planning (Zimmermann and Lappe 2016). A possible common explanation of the effect of SA on localization (Zimmerman and Lappe 2010) and on attention (Habchi et al. 2015) is a SA-induced compression of represented visual space (in case of backward adaptation) that would shift the representation of visual stimuli toward the center of gaze. Consequently, when subjects have to localize (Zimmermann and Lappe's) or simply detect (current study and Habchi et al.'s) such stimuli with no eye movement allowed, they would both underestimate the targets' eccentricity and detect them with a faster RT. Further studies are required to fully address our hypothesis on the nature of GBA increase in the left hemisphere. For example, eliciting forward adaptation of leftward saccades should, following this rationale, elicit a GBA increase observed in sensorimotor cortex of the right hemisphere (related to the leftward bias of saccade aiming error) and in the right superior parietal lobule (related to the leftward saccadic vector).

Finally, we think that other cognitive processes sharing the same substrates as SA could benefit from this GBA increase. Indeed, it has been extensively demonstrated that increased behavioral performances are related to both poststimulus-induced GBA (Fries et al. 2001) and prestimulus-ongoing GBA (e.g., Hoogenboom et al. 2010). Also, GBA has been causally related to increase in performance in a neurofeedback study showing a subsequent beneficial effect of the GBA increase on perceptual performances (Salari et al. 2014).

To conclude, by conducting the first study in humans of the electrophysiology of oculomotor plasticity, we highlighted that GBA can be entrained in a large cortical network. This GBA modulation could be beneficial to other overlapping cognitive processes, opening new perspectives of rehabilitation of different cognitive impairments such as neglect.

Supplementary Material

Supplementary material is available at *Cerebral Cortex* online.

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Notes

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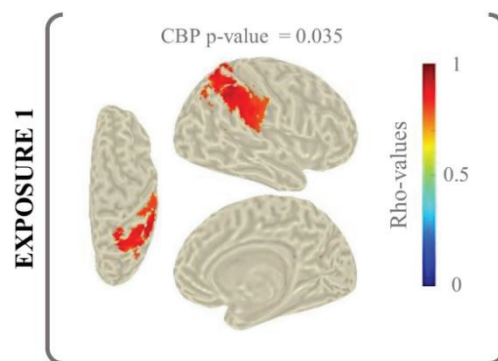
1.2. Supplement

Supplementary methods

On the one hand, to quantify SA behavior, the amount of saccadic adaptation during the three saccadic exposure blocks was first computed for each subject as the mean saccadic gain change between each exposure block and the pre-exposure phase, separately in adaptation and in control sessions. The relative gain change in the control session was then subtracted from the relative gain change in the adaptation session. On the other hand, to extract the GBA change specifically related to SA, we computed, again separately for each subject and exposure block, the difference of GBA power between the % Adaptation Exposure and % Control Exposure (frequency range: 75 ± 15 Hz, time window: from 400 ms to 100 ms pre-target). Finally, the Spearman correlations between these two variables (SA behavior and specific GBA change) were calculated at the source level and their significance assessed using a cluster-based permutation analysis.

Supplementary results

We found that the GBA during exposure 1 of the adaptation (during which nearly 50% of the adaptation is achieved, Fig. 3) significantly correlated with the amount of SA. Namely, the more saccadic gain change, the more gamma power as compared to the pre-exposure saccadic task. At the source level, we found a cluster with a cluster threshold of 0.001 and a p-value of 0.035. This cluster was centered on the right parietal lobe (see Supplementary Fig. 1). These results are considered as exploratory and should be treated with caution as the rho values reported here are likely inflated given the group size (Yarkoni, 2009). Given this caveat, we found interesting to report that the parietal cortex seems to be activated during exposure to saccadic adaptation.



Supplementary Figure 1: Correlation across subjects between relative gain change and gamma band power relative change during Exposure 1. Rho-values distributions, masked at $P=0.05$, are displayed on surface cortical maps.

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2. Study 2: Effect of RS adaptation on exogenous attention

2.1. Main article

Title: “Reactive saccade adaptation boosts exogenous orienting of visuospatial attention”

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ABSTRACT

Attention and saccadic eye movements are critical components of visual perception. Recent studies propelled the hypothesis of a tight functional coupling between saccadic adaptation (SA) and attention: SA increases the processing speed of unpredictable stimuli (Habchi et al., 2015a), while increased attentional load boosts SA (Gerardin et al., 2015). Moreover, their cortical substrates partially overlap (Gerardin et al., 2012; Corbetta et al., 2008).

Here, we investigated for the first time whether this functional coupling in the reactive/exogenous modality is specific to the orienting system of attention. We studied the effect of adaptation of reactive saccades (RS), elicited by the double-step paradigm (McLaughlin, 1967), on exogenous orienting, measured using a Posner-like detection paradigm (Posner, 1980). In 18 healthy subjects, the attentional benefit - the difference in reaction time to targets preceded by informative versus uninformative cues - was compared between the pre- and post-phases of leftward RS exposure to: backward adaptation, forward adaptation, or control (no-adaptation). We found that, when a cued-target was presented in the left hemifield, the attentional benefit significantly increased after backward SA, but neither after forward SA nor after control. These findings provide strong evidence in humans for a functional coupling between RS adaptation and exogenous attention, possibly through the activation of a common neuronal pool, and open rehabilitation perspectives for patients with visuospatial disorders.

KEYWORDS

Oculomotor plasticity, Visuospatial attention; Exogenous orienting; Reactive saccades

1. Introduction

Human beings make from 150 000 to 200 000 ocular saccades every day. These rapid eye movements are categorized as either (1) reactive saccades (RS) that are triggered by the sudden appearance of a stimulus, or (2) voluntary saccades (VS) that are intentionally driven to explore a stable environment (Gaymard, Ploner, Rivaud, Vermersch, & Pierrot-Deseilligny, 1998). Both types of saccade rely on partially overlapping substrates. Saccades are critical components of visual perception, and therefore any saccadic inaccuracy can result in visual impairment (Leigh & Zee, 1999). Fortunately, saccade accuracy is maintained throughout the entire life thanks to visuo-oculomotor plastic processes known as saccadic adaptation (SA). Saccadic adaptation is elicited by repeated alterations of the efficacy of motor commands due to growth, fatigue, aging and, to a certain extent, neurological pathologies or injuries (for review: Pélisson, Alahyane, Panouillères, & Tilikete, 2010). It can also be elicited in the laboratory thanks to the double-step paradigm introduced by McLaughlin (1967), allowing to study SA as a good model of sensorimotor plasticity. For a long time, SA neural substrates were thought to be restricted to the cerebellum and cerebellar-recipient brainstem areas (Takagi, Zee, & Tamargo, 1998; Desmurget, 1998; Barash et al., 1999; Straube, Deubel, Ditterich, & Eggert, 2001; Prsa & Thier, 2011; Panouillères, Miall, & Jenkinson, 2015). But recently, evidence has accumulated in favor of an involvement of the cerebral cortex in saccadic adaptation. First, the transient impairment of the cortex at the level of IntraParietal Sulcus (iPS) with single pulse TMS interferes with VS adaptation and tends to facilitate RS adaptation (Panouillères et al., 2014). Second, VS adaptation leads to a metabolic activation revealed by fMRI of the medial and posterior IPS as well as of the inferior precentral sulcus (iPrCS) whereas RS adaptation is associated with activation of the temporo-parietal junction (TPJ), area V5 and iPrCS (Gerardin et al., 2012). Third, in two other fMRI studies, RS adaptation resulted in BOLD fluctuations in the supplementary eye field (SEF), the temporal lobe, and the posterior insula (Blurton, Raabe, & Greenlee, 2012) or in the dorsolateral and dorsomedial cortical areas in the frontal and parietal lobes including the precuneus (Guillaume, Fuller, Srimal, & Curtis, 2018).

Besides its role in oculomotor responses *per se*, SA is crucial for visual perception. Indeed, saccadic adaptation contributes to perceptual performance indirectly by optimization of visual feedback thanks to accurate eye scanning. But importantly, SA might also play a more direct role on visual processes such as visuospatial attention. Visuospatial attention enhances the efficiency of processing of visual signals originating from the area of space where it is focused on, and simultaneously decreases processing of signals coming from locations situated outside this attentional locus (Posner, 1980) (Carrasco, Penpeci-Talgar, & Eckstein, 2000). Movements of our attention focus either without or with saccadic eye movements (covert and overt attention shifts, respectively) allow us to explore our environment

Experimental contributions

according to its content and to our internal goals. Accordingly, and similar to the two types of saccades (RS and VS), covert shifts of attention can be automatic, in reaction to the sudden appearance of a visual stimulus (exogenous shift of attention), or can be intentionally driven (endogenous shift of attention).

Covert shifts of attention and saccadic eye movements share several other features. In the framework of the premotor theory of attention, the former are considered to be identical to unexecuted saccades due to inhibition at the oculomotor output level (Rizzolatti, Riggio, Dascola, & Umiltá, 1987; Smith & Schenk, 2012). It has been shown that when a change occurs somewhere in the visual field, it first attracts one's attention, and, a bit later, one's gaze. Saccades cannot be made without such pre-saccadic shift of attention (Deubel & Schneider, 1996; Kowler, Anderson, Doshier, & Blaser, 1995; Deubel, 2008; Smith & Schenk, 2012). Conversely, one generally makes saccades toward the currently attended location, like the target of a goal-directed limb movement (Neggers & Bekkering, 2000). The overlap of oculomotor and attention neural systems has also provided a strong support to the premotor theory of spatial attention. Neuroimaging and transcranial magnetic stimulation (TMS) studies in humans have shown that attending covertly to a peripheral location or preparing to move the eyes toward this location activates the same neural network of frontoparietal regions (Smith & Schenk, 2012; Smith, Schenk, & Rorden, 2012). Furthermore, quite interestingly, not only the cortical saccade substrates overlap with visuospatial attention but the cortical substrates of SA, which have been recently investigated (Gerardin et al., 2012: see above) also do. In addition, they share with those of attention orientation (Corbetta & Shulman, 2002; Corbetta et al., 2008) a marked endogenous versus exogenous segregation: indeed both VS and endogenous attention involve the IPS whereas RS and exogenous shifts of attention both recruit the rTPJ.

The strongest argument for a functional coupling between attention and saccades is provided by the demonstration that these two processes can impact on each other. A few recent studies support this idea. First, SA efficiency has been reported to increase with attentional load (Gerardin et al., 2015) showing that modifications of visuospatial attention can impact SA efficiency. Second, Habchi and colleagues (2015) reported that saccadic adaptation of reactive saccades towards the left hemifield increased the processing speed of unpredictable stimuli presented in this left hemi-field, whereas no such modification was detected in the opposite hemifield, nor in a control session where subjects performed the same reactive saccades but with no adaptation induced. Finally, we recently reported that adaptation of leftward RS impacts the brain excitability, as reflected by an increase of the gamma band power (i.e. fast cortical activity), in a wide network including the ventral stream of exogenous shift of attention (Nicolas et al., 2018). However, note that the visual detection task used in these two studies did not allow to specifically isolate covert attention shifts from other cognitive or motor components

potentially involved and, in the second study, did not disclose any significant behavioural effect of RS adaptation.

This present study aims at providing definitive evidence for the existence of a coupling between SA and covert attention and at deepening our understanding of this coupling. Based on the evidence reviewed above, we suggest that the brain activity modulations related to the development of RS adaptation in the ventral stream of exogenous attention (Nicolas et al., 2018) will lead to an increased performance in a task requiring exogenous orienting of attention and thus relying on this ventral stream. We focused on the adaptation of leftward reactive saccades and investigated backward as well as forward adaptation which are subtended by different mechanisms (Panouilleres et al., 2009). We designed a Posner-like paradigm (Posner, 1980) to specifically measure the orienting of exogenous attention and the effect of SA thereon. The attentional index or cue benefit (difference in reaction time between trials with an informative cue and trials with an uninformative cue) was measured for each subject before and after exposure to backward-adapted, forward-adapted, or non-adapted (control) leftward saccades.

2. Materials and Methods

2.1. Subjects

The experiment adheres to the code of ethics of the World Medical Association – Declaration of Helsinki of 2008 and received the approval of the Ethics Committee of INSERM (CEEI - IRB 00003888, n°16-305). All the twenty-three subjects were paid for their participation. Among these 23 subjects, four were excluded because they did not show any significant gain modulation related to saccadic adaptation exposure and one subject because answering too often (NO-GO false alarm > 20%) in ‘NO-GO trials’. The 18 remaining subjects comprised 17 right-handed subjects and 10 females (mean age 26.11 +/- 4.64 *SD*, Standard Deviation). Their vision was normal or corrected-to-normal vision. Criteria of exclusion were: neurological or psychiatric disorders history; cognitive disorders preventing the comprehension of the instructions; severe sleep deprivation during the last 24 hours; consumption of psychotropic drugs, substances, or alcohol during the last 24 hours; participation to other experiments involving sensorimotor adaptation during the last week. After written consents obtained, each subject was assigned pseudo-randomly to one of the six sub-groups, corresponding to the 6 possible orders of testing in the three experimental sessions (within-subject design, see General Design section). The number of subjects was determined from a power analysis performed through the G*Power software (Faul, Erdfelder, Lang, & Buchner, 2007) and based on parameters established from the literature and from pilot data (see Power analysis in the Supplementary Methods in the APPENDIX).

2.2. Apparatus, stimuli and procedure

2.2.1. Apparatus

The whole experiment was carried out in a dimly lit room. Subjects were installed in a comfortable position with the head stabilized by a chin-rest, cheekbone rests, and forehead support; they faced a computer screen (1920 x 1080 pixels; 53.5 x 34.5 cm; 144 Hz refresh rate) at 57 cm from their eyes. The experiment is timed based on the 144 Hz refresh rate of the computer display (frame duration approximately 7 ms), therefore all time intervals reported in the following represent multiple of the frame duration and are rounded to the nearest value in milliseconds. Psychopy, an open-source software, was used for the stimuli presentation and data collection in all different tasks (Peirce, 2008). Movements of the right eye were recorded at a frequency of 1000 Hz using the remote configuration of the EyeLink 1000 infrared tracker (SR research, Canada). Each task started with the calibration of the eye tracker by asking subjects to fixate a series of 5 targets displayed near the borders and at the center of the screen.

2.2.2. General design

All subjects were submitted to three experimental sessions, each of which ('backward adaptation', 'forward adaptation' and 'control') comprising identical pre-exposure and post-exposure phases as well as a specific exposure phase (Figure 1). In the backward and in the forward adaptation conditions, the exposure phase consisted in adaptation of leftward saccades (decrease or increase of saccadic gain, respectively) without adaptation of rightward saccades, whereas during the exposure phase of the control condition, saccades in both directions were not adapted. One fifth of the saccades during the exposure were rightward (randomly inserted) to reinforce the reactive modality with the uncertainty of the target side appearance. The control session provided a baseline measure of saccades and of visuospatial attention shifts to both the left and right hemifields, thus allowing specific assessment of the effects of saccadic adaptation induced in the backward and forward adaptation sessions. These effects on saccade and on attention were measured, by comparing between the pre- and post-exposure phases of each session, subjects' performance respectively in a test saccade task (to verify successful saccadic adaptation) and in a visual detection attentional task. The delay between each session was at least 14 days in order to avoid any retention of saccadic adaptation between sessions, based on a previous study disclosing a significant retention of adaptation up to 5 days after exposure but not 11 days after (Alahyane & Pélissou, 2005).

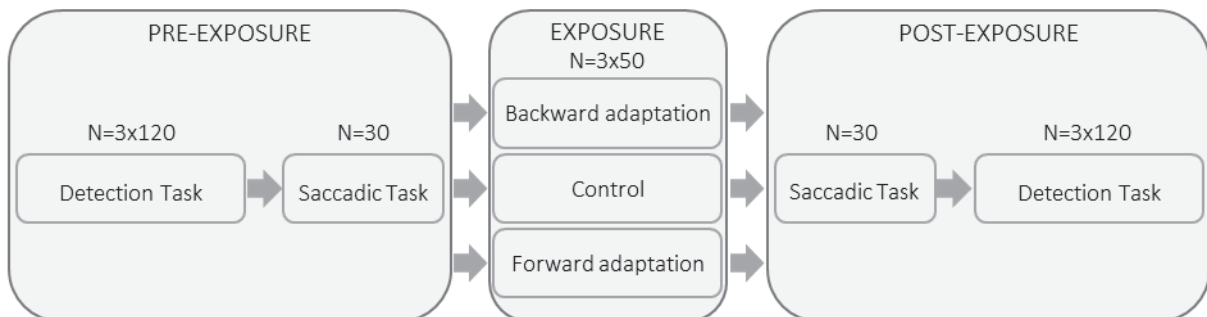


Figure 1: Study general design. Each subject underwent 3 experimental sessions, differing only by the Exposure phase (either backward adaptation, forward adaptation or control). N = number of trials.

2.2.3. Saccadic tasks

The saccadic adaptation exposure task was performed using a modified version of the double-step paradigm introduced by (McLaughlin, 1967). This paradigm consists in displacing the visual scene while the subject is executing a saccade towards a peripheral target. Thanks to the saccadic suppression phenomenon, this intra-saccadic visual displacement is usually not consciously perceived by subjects

Experimental contributions

and leads to a mismatch between post-saccadic eye fixation and target location which is interpreted by the central nervous system as a saccade aiming error.

Sequence of events in adaptation trials (Figure 2B-C-D). One fixation dot of 0.3° of visual angle was displayed at the center of the computer screen. The subject had to fixate this dot during a pseudo randomized delay of 301 ms to 701 ms after which the central dot disappeared and simultaneously a peripheral target appeared at 11° of eccentricity aligned with the horizontal meridian, either to the left or to the right. The side of the peripheral target was randomly assigned between the adapted direction (leftward) and the opposite un-adapted direction (rightward). The subject had to initiate a saccade towards the peripheral target and was instructed to be as fast and precise as possible. Correct eye fixation of the central dot was ensured by continuous monitoring of the eyetracker signal. The reactive saccade was detected when the eye velocity was higher than $70^\circ/\text{s}$ (for detailed algorithm: Dalmajer, Mathôt, & Van der Stigchel, 2014). When the peripheral target was in the adapted hemifield this event triggered a 4° -shift of the visual scene (jumping to a 7° or 15° of eccentricity for the backward or forward exposure conditions; Fig. 2C and 2D respectively), whereas when presented in the un-adapted hemifield the peripheral target remained at the same location (Figure 2B). The visual scene (shifted or not) remained visible for 805 ms after the detection of the saccade. Subjects were instructed to look at the peripheral target until it turns off. The subjects then had a delay of 1000 ms to blink and look back to the central dot. The next trial started as soon as fixation around the central dot location was detected.

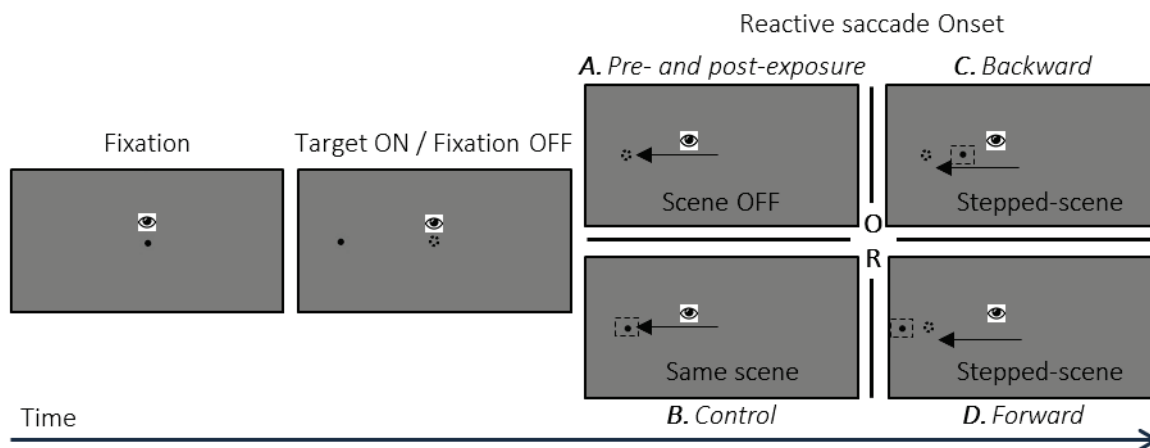


Figure 2: Time-line of trials in the saccadic tasks (not to scale). Subjects were instructed to initiate a saccade as fast and as precise as possible as soon as, after a random fixation period, the central dot is replaced by a peripheral target (11° of eccentricity, to the left in this example). Then, different events occurred upon detection of the reactive saccade, depending on the following conditions. **A.** In the pre- and post- saccadic phase, the visual scene was turned off, **B.** In the control condition of the exposure phase, the visual scene remained at the same position **C.** In the backward condition of the exposure phase, the visual scene was shifted 4° backward (final eccentricity: 7°). **D.** Finally, in the forward condition of the exposure phase, the visual scene was shifted 4° forward (final eccentricity: 15°). In all cases, subjects were instructed to keep looking at the peripheral target position for ~ 1 sec and then look back to the center in anticipation of the fixation point re-appearance, using this return period to blink if necessary.

The saccadic control task, also referred to as the control exposure, was identical to the adaptation task except that there was no jump of the visual scene in any of the trials ('Control' in Fig. 2B), thus both rightward and leftward control trials were identical to the adaptation exposure trials towards the unadapted hemifield.

For all sessions, the exposure phase of 150 trials consisted in 3 blocks of 50 trials each (10 with a right target and 40 with a left target). Between each block, the subject was allowed to rest with the head still as long as needed.

To maximize subjects' involvement and motivation throughout the saccadic tasks, they were requested to perform in parallel an easy detection task: in random trials (from 5 to 20 per block), the peripheral target contained a white dot of 0.008° of visual angle (not detectable in peripheral vision but easy to detect after the saccade to the target), and the subject had to push a button whenever they detected a white dot. The performance was indicated to subjects during the rest period between the blocks but was not further analyzed.

Pre- and post-exposure saccadic tasks (Figure 2A). These tasks were identical to the exposure task except that the visual scene did not jump but instead was turned off at the initiation of the saccade. Each task consisted in one block of 30 trials (15 with a right target and 15 with a left target, randomly ordered). Comparison between pre- and post-exposure tasks allowed measurement of the adaptation after-effect and thus quantitative assessment of the adaptation strength.

2.2.4. Attention task: detection

Covert orienting of exogenous attention was elicited using a variant of the Posner task (Posner, 1980) designed with general settings (a peripheral cue, and a short SOA) appropriate for shifts of exogenous attention. In the present task, contrasting between informative, 100% valid cues (informative trials), and uninformative cues (uninformative trials), allowed us to measure the pure benefit of exogenous orienting whereas, in most exogenous attention studies, the contrast is calculated between valid and invalid cues and thus reflects the cumulated effect of costs and benefits (Chica, Bartolomeo, & Lupiáñez, 2013; Chica, Martín-Arévalo, Botta, & Lupiáñez, 2014). A typical trial is illustrated in Figure 3. A fixation cross subtending 1° of visual angle appeared at the center of the screen (grey 50%) at the beginning of the trial and remained visible until the subject's response, and the subject had to keep eye fixation on that location all throughout the trial. Eight light grey (35%) empty placeholders (squares of 1.75° of visual angle) were also presented along the horizontal meridian, on the left and on the right, at 3° , 7° ,

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11°, and 15° of eccentricity. After a pseudo-randomized (98 to 292 ms) delay from the beginning of the trial, a cue appeared for 98 ms. This cue consisted in highlighting the placeholders in red. For two thirds of the trials (80 ‘informative trials’ out of 120 trials for each block) the cue validly informed the future target location: only one square was highlighted, being predictive of the upcoming target location. In 40 ‘uninformative’ trials (one third), the cue did not provide any spatial information about the upcoming target, consisting of the eight placeholders turning red. This 2:1 informativeness ratio was meant to reinforce the validity of the cue (Bidet-Calet, Bottemanne, Fonteneau, Giard, & Bertrand, 2015). In all trials, the cue period was followed by a random time of 98 to 292 ms after which one grey dot (diameter: 0.3°) appeared for 49ms. The subjects were instructed to detect this grey dot as fast as possible. The maximum duration for detection was 1500 ms after which the trial ended. Each trial was followed by a blank interval of 1001 ms. Eye fixation was continuously monitored during the trial and whenever the subject stopped fixating (gaze deviating from the fixation cross by more than 1.5° in any direction), the fixation cross immediately turned red and the trial was aborted. Aborted trials were replayed back during the same block of trials.

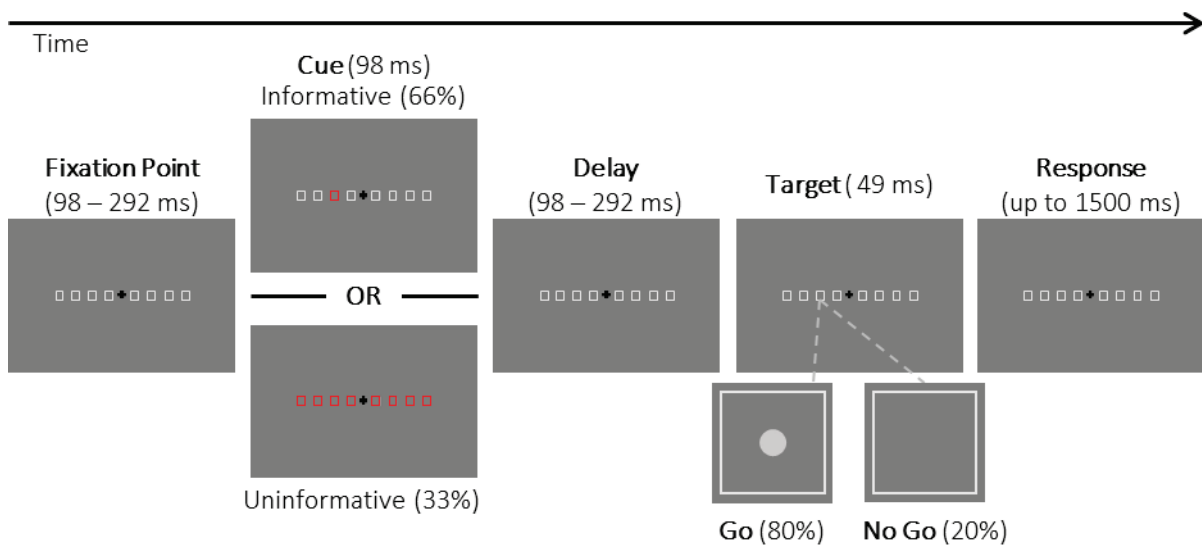


Figure 3: Time-line of trial in the detection task (not to scale). A central fixation cross and 8 lateral empty placeholders (eccentricity: 3°; 7°; 11°; 15° in each hemifield), were displayed at the beginning of the trial. Then placeholders turned red for 98 ms, either indicating the square of the upcoming target (informative cue), or providing no spatial information (uninformative cue). The target presented after 98 to 292 ms of delay consisted in the brief appearance (49 ms) of a grey dot on either side (left 50% or right 50%). Subjects had to respond as fast as possible by pushing a lever when a target was present (Go: 80%) or to refrain from responding when there was no target appearing (No Go: 20%).

The tasks consisted of 3 blocks of 120 trials each (360 in total): 32 ‘informative - left target’, 32 ‘informative - right target’, 16 ‘uninformative - left target’, 16 ‘uninformative - right target’, and 24 ‘No-Go’ trials (proportionally distributed among trial conditions). The ‘No-Go’ trials were then excluded from

the analysis. Subjects answered by pushing away with their index finger a lever-switch in their mid-sagittal axis.

2.3. Data analyses

Data analyses were performed with the open-source software R (The R Core Team, 2013). These analyses concerned the saccadic behavior during the pre- and post-exposure saccadic tasks as well as the performance in the detection tasks. The latter was expressed as a cue benefit, measured by the relative change between informative and uninformative median RT. Any exclusion of a subject due to criteria described in the following paragraphs led to his/her replacement.

2.3.1. Saccadic tasks

2.3.1.1. Pre-processing

The eye movement data were analyzed off-line using custom software developed in Matlab (Math Works Inc., Natick, MA, USA). The beginning of the primary horizontal saccade was identified based on a velocity threshold of $30^{\circ}.s^{-1}$. Saccadic amplitude was measured as the difference between eye positions 50 ms before the saccade onset and 50 ms after the saccade offset. The main dependent variable in the saccadic tasks was the saccadic gain, computed as the ratio between saccadic amplitude and initial target eccentricity (difference between target position and starting position of the saccade). Saccades with a gain less than 0.5 or outside the mean ± 2 *SD* interval were discarded from further analysis.

2.3.1.2. Statistical analysis

Since the saccadic adaptation was critical to test our hypothesis, we excluded from the main analysis subjects who did not show the expected decrease (backward exposure) or increase (forward exposure) of saccade gain in the adapted hemifield. To this aim, we first performed, separately for each subject and each hemifield, a unilateral Student t-test comparing the saccadic gain between the pre- and the post-saccadic tasks and used a threshold *p*-value of 0.05 after FDR-correction for 6 multiple comparisons. Moreover, for representational purposes, we computed the exposure after-effect for each hemifield and each exposure condition as follow:

$$\begin{aligned} & \textit{Exposure after} - \textit{effect}_{\textit{exposure of interest}} \\ &= \frac{\textit{mean gain}_{\textit{post-exposure}} - \textit{mean gain}_{\textit{pre-exposure}}}{\textit{mean gain}_{\textit{pre-exposure}}} \end{aligned}$$

A negative exposure after-effect reflects a decrease of the saccadic gain between the pre- and the post-exposure phases whereas a positive after-effect reveals an increase.

Finally to calculate the effect size (Cohen's d) of the SA after-effect in the backward and the forward exposure sessions, we computed the mean of the gain for each subject, in the left hemifield for the pre-exposure and the post-exposure phases separately.

2.3.2. Attention task

2.3.2.1. Pre-processing

To ensure that the involvement level of all subjects was high, and to exclude those with a too low global performance or too high fluctuations, each session were divided in 24 experimental cells of conditions: 2 Cues (informative or uninformative) x 2 target Hemifields (left or right) x 2 Phases (pre- or post-exposure) x 3 Blocks (smallest cell = 16 trials). None of the subjects had a number of correct 'Go' trials inferior to 8 for any of these cells. Outliers RT of correct trials were excluded using the John Tukey's method of leveraging the Interquartile Range. Then, the median Reaction Time (RT) of those correct and in-range trials was computed in each of these cells. If one cell's median RT lied outside $\pm 3 SD$ (Standard Deviation) from the subject's average of median RTs computed across the 24 cells, the subject was excluded.

2.3.2.2. Outcome neutral criteria

First of all, a significant difference between the informative trials and uninformative trials in the pre-exposure phase was a prerequisite to demonstrate that, at the group level, our discrimination task readily engaged the orienting of exogenous attention. For that purpose, a 2-way rmANOVA was performed on detection RT of pre-exposure phases, with Cue as 2-level factor (informative or uninformative) and Exposure as 3-level factor (control, backward adaptation, or forward adaptation exposures). The critical outcome neutral condition was a main cue effect. Also, the lack of Exposure effect as well as of interaction between the Cue and the Exposure factors would allow us to check that, ideally, both the pre-exposure RTs and the pre-exposure RT differences (informative versus uninformative) do not differ between the three conditions

2.3.2.3. Statistical analysis

For this analysis, the dependent variable was the subjects' cue Benefit which was computed as follow:

$$Cue\ benefit_{exposure\ of\ interest} = \frac{RT_{Uninformative} - RT_{Informative}}{RT_{Informative}}$$

This dependent variable was computed in the 36 experimental cells defined from the factors of the rmANOVA with subjects as the repeated measure, the target Hemifield (left or right), the Block of the task (first, second, or third block), the Phase (pre- or post-exposure) and the Exposure (backward adaptation, forward adaptation, or control) as within-factors.

This rmANOVA revealed a significant four-level interaction and was thus followed by post-Hoc analyses. To this aim, we ran rmANOVA on data from the left and right hemifields separately with the Exposure, the Phase, and the Block as within-factors. These two tests were then FDR corrected (2 tests). (1) On the one hand, the right hemifield analysis disclosed a significant interaction between the Exposure and the Phase, and was thus followed by 3 Student *t* tests (one per exposure) comparing the cue effect between pre- and post-exposure phases in the right hemifield and FDR-corrected for 3 tests. (2) On the other hand, the left hemifield analysis disclosed a significant interaction between the Exposure, the Phase, and the Block. To decipher this triple interaction we first ran 3 separate rmANOVA (one per block) with the Exposure and the Phase as within-factors and FDR corrected for 3 tests. These tests revealed an interaction between the Exposure and the Phase for blocks 1 and 3. We thus conducted 3 Student *t* tests for each of these blocks (FDR-corrected for 3 tests), each *t* test comparing the cue benefit between the pre- and the post-exposure phases in each exposure condition.

To evaluate the spatiality of the highlighted effect for the control exposure (see Statistical analysis of the Detection task in the Results section 3.2.2), we ran a rmANOVA on the control data with the Phase and the Hemifield as within-factors.

Finally, we further evaluated the effect found after backward adaptation (in block 3) on cue benefit in the left hemifield (see Results). We first check that the target eccentricity factor did not interact with this boosting effect, by submitting to a rmANOVA the left hemifield cue benefit from the third block of backward exposure with target eccentricity and Phase as within factors. We then sought for a correlation (Pearson's product-moment correlation) between the saccadic after-effect of backward adaptation (see formulae above) and the relative change of cue benefit in the left hemifield between the pre- and the post-exposure of leftward adaptation, calculated as follows:

$$Relative\ Change_{Cue\ benefit} = \frac{Cue\ benefit_{post-exposure} - Cue\ benefit_{pre-expsoure}}{Cue\ benefit_{pre-expsoure}}$$

3. Results

3.1. Pre- and post-exposure saccadic tasks

After rejection of trials following the above mentioned criteria (see Pre-processing of the saccadic task in the MATERIALS & METHODS section 2.3.1.1), the average number of trials per condition was 13.8 +/- 1.3 SD (total number of trials = 15). The mean saccadic gain in pre- and post-exposure, as well as the individual and mean adaptation after-effect, are illustrated in Figure 4. As it was a prerequisite, all subjects showed a significant modulation of the saccadic gain for target presented in the left hemifield in the post-exposure as compared to the pre-exposure (decrease after backward exposure, increase after forward exposure), thus having a significant after-effect due to SA (Figure 4 right panel). Moreover, as seen in Figure 4 (left panel), this decrease was not seen in the opposite, un-adapted, hemifield, neither for the backward nor for the forward exposure. In addition no gain change in either hemifield took place in the control exposure.

Noteworthy, the magnitude of the effect was different between the backward (cohen's $d = 1.69$) and the forward (cohen's $d = 1.23$) adaptation, an effect that is well documented in the literature (see for review (Pélisson et al., 2010).

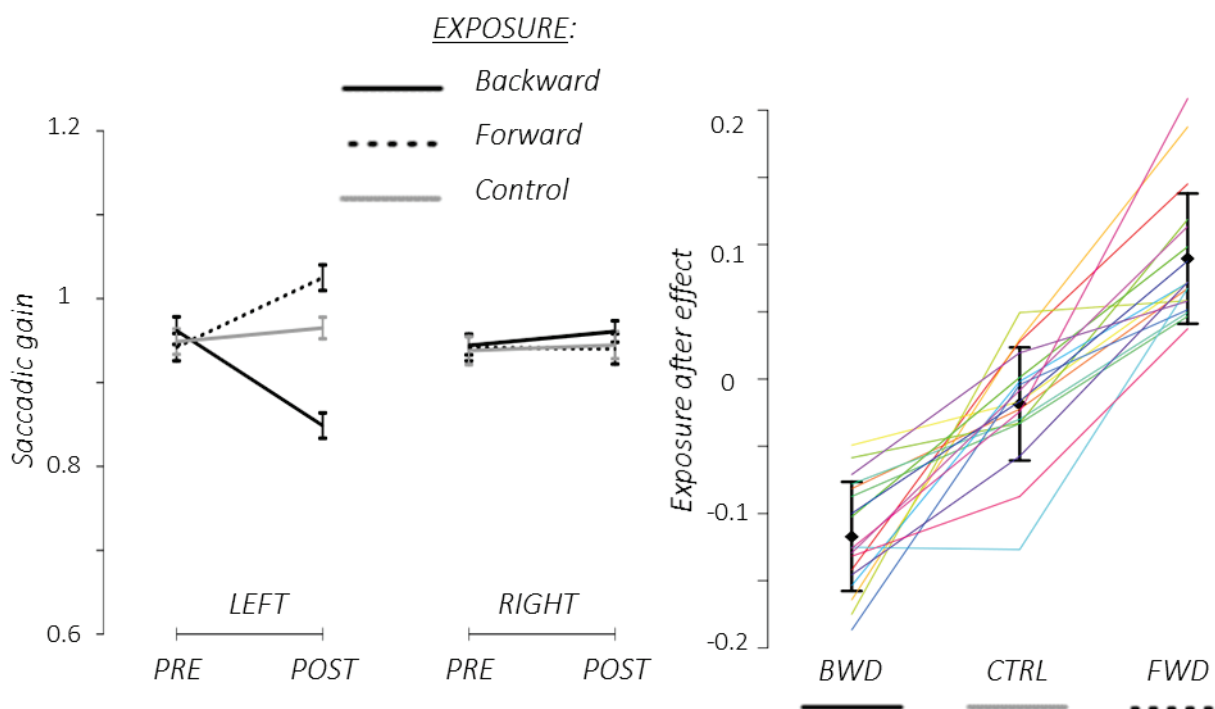


Figure 4: Pre- and Post-exposure saccadic task results. **Left panel:** Group mean (+/- SD) of saccadic gain. Black lines: backward adaptation exposure; Black dotted: forward adaptation exposure; Grey lines: control exposure. **Right panel:** Individual after-effects. Solid black lines represent group mean (+/- SD) and colored lines stand for individual values.

3.2. Attention task

3.2.1. Outcome neutral criteria

After rejection of trials following the above mentioned criteria (see Pre-processing of the attention task in the MATERIELS & METHODS section 2.3.2.1), the average number of trials per condition was 27.78 \pm 2.47 *SD* for the informative trials (total number of trials = 32) and 14.32 \pm 1.33 *SD* for the uninformative trials (total number of trials = 16).

The rmAnova of outcome neutral criteria on the pre-exposure RT revealed a significant main effect of the Cue validity (partial $\eta^2 = 0.80$; $F_{(1,17)} = 69.20$; $p = 2.14e^{-7}$; achieved power = 1, Figure 5). The main effect of the Exposure was not significant (partial $\eta^2 = 0.09$; $F_{(2,34)} = 1.78$; $p = 0.18$), nor the interaction between Exposure and Cue validity (partial $\eta^2 = 0.08$; $F_{(2,34)} = 1.41$; $p = 0.26$). Therefore, the Posner-like discrimination task did engage the exogenous orienting of attention. Moreover, neither the RTs nor the informative versus uninformative RT differences significantly differed between our three sessions before the exposure.

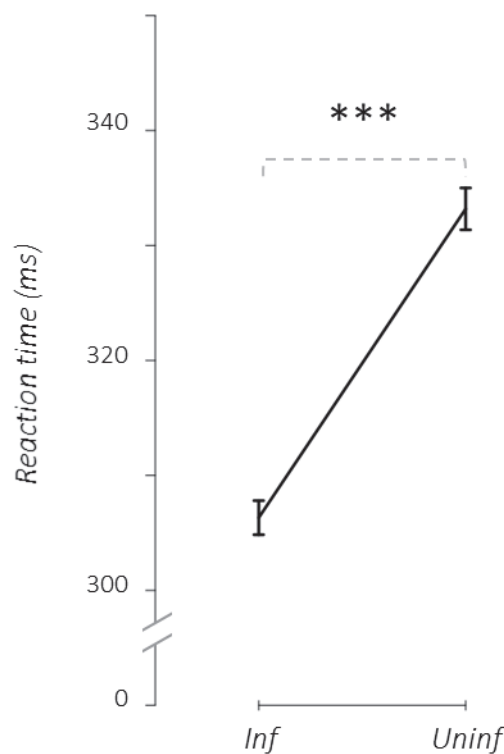


Figure 5: Pre-exposure cue effect on the reaction times in the attention task. Group mean (\pm SD) of median reaction time (ms). A general decrease of the RT for the informative trials as compared to the uninformative trials can be observed.

3.2.2. Statistical analysis

The performance in the detection task was evaluated by computing the cue benefit (see Methods) **Figure 5**. The 4-factor rmANOVA (Exposure x Phase x Block x Hemifield) revealed no significant main effect, nor double, nor triple interaction. Conversely, the interaction Exposure x Phase x Block x Hemifield was significant (partial $\eta^2 = 0.17$; $F_{(4,68)} = 1.59$; $p = 0.01$), as presented in Figure 6.

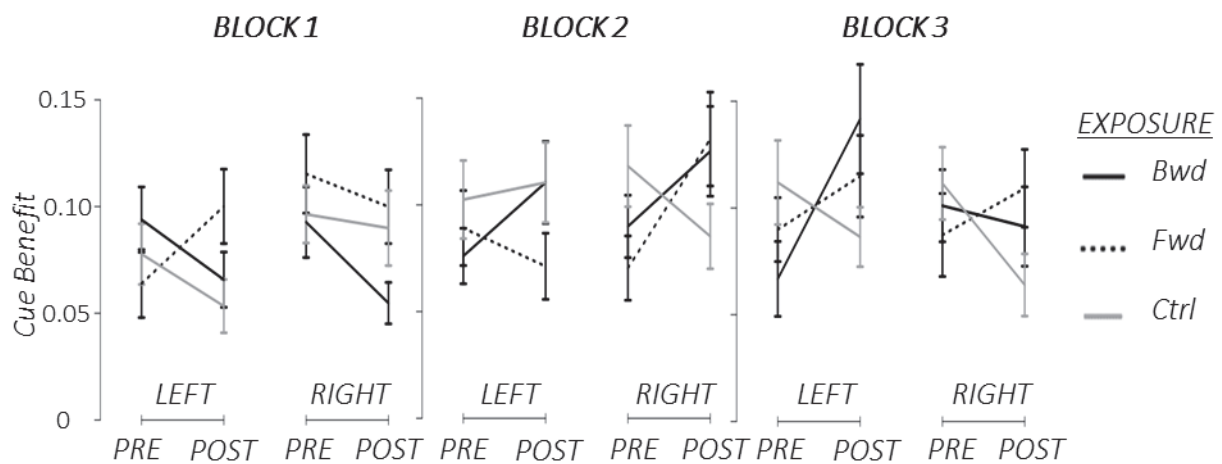


Figure 6: Pre- and Post-exposure results in the attention task for each Block. Group mean (\pm SD) of cue benefit for the pre- and the post-exposure phases in the two hemifields of target presentation. Black lines: backward adaptation exposure; Black dotted: forward adaptation exposure; Grey lines: control exposure.

First, in the right hemifield, the post-Hoc 3-factor rmANOVA (Exposure x Phase x Block) on the cue benefit (Figure 7, left panel) revealed only a significant Exposure x Phase interaction (partial $\eta^2 = 0.22$; $F_{(2,34)} = 4.82$; $p = 0.01$, FDR-corrected $p = 0.01$). The following student t tests comparing pre- and post-exposure benefit in each exposure condition revealed that the cue benefit significantly decreased after control exposure ($t_{(215)} = 2.66$; $p = 8.41e^{-3}$; cohen's $d = 0.21$), whereas no significant difference in the other exposures was found (Backward: $t_{(215)} = 0.32$; $p = 0.75$; Forward: $t_{(215)} = -1.49$; $p = 0.14$).

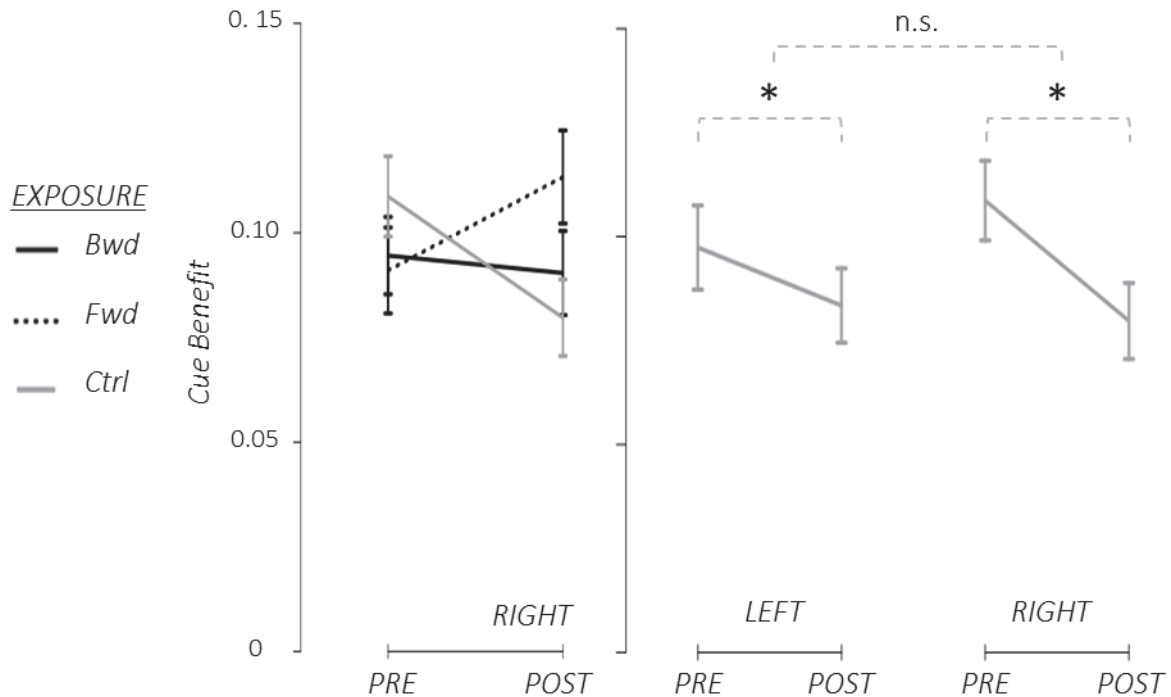


Figure 7: Pre- and Post-exposure results showing the decrease of cue benefit after control exposure. Group mean (\pm SD) of cue benefit. **Left panel:** right hemifield data for all three exposure conditions (Black lines: backward adaptation exposure; Black dotted: forward adaptation exposure; Grey lines: control exposure). **Right panel:** Control exposure data for both hemifields (post Hoc analysis on the hemifield specificity of the cue benefit decrease).

Second, in the left hemifield, the post-Hoc 3-factor rmANOVA (Exposure x Phase x Block) on the cue benefit (Figure 6) only revealed a significant triple interaction Exposure x Phase x Block (partial $\eta^2 = 0.19$; $F_{(4,68)} = 4.03$; $p = 5.44e^{-3}$, FDR-corrected $p = 0.01$). The post-Hoc rmANOVAs on block 1 and block 3 revealed a nearly significant double interaction Exposure x Phase; whereas the block 2 did not (block 1: partial $\eta^2 = 0.21$; $F_{(2,34)} = 4.41$; $p = 0.02$; FDR-corrected $p = 0.06$; block 2: partial $\eta^2 = 0.06$; $F_{(2,34)} = 1.13$; $p = 0.35$; FDR-corrected $p = 0.06$; block 3: partial $\eta^2 = 0.17$; $F_{(2,34)} = 3.60$; $p = 0.04$; FDR-corrected $p = 0.06$). The rmANOVA on block 3 data also revealed a main effect of the Phase (partial $\eta^2 = 0.24$; $F_{(1,17)} = 5.25$; $p = 0.03$), however, since this factor is involved in an interaction we won't discuss further this result. Student t test comparing pre- and post-exposure cue benefit in each exposure condition for the data of block 1, did not revealed significant modulation of the cue benefit between the pre- and the post-exposure phases for any of the exposure conditions (p -values > 0.13). For the block 3 instead, Student t test revealed that the cue benefit significantly increased after backward adaptation ($t_{(71)} = 2.66$; $p = 0.02$; FDR-corrected $p = 0.05$; cohen's $d = 0.40$) (Figure 8).

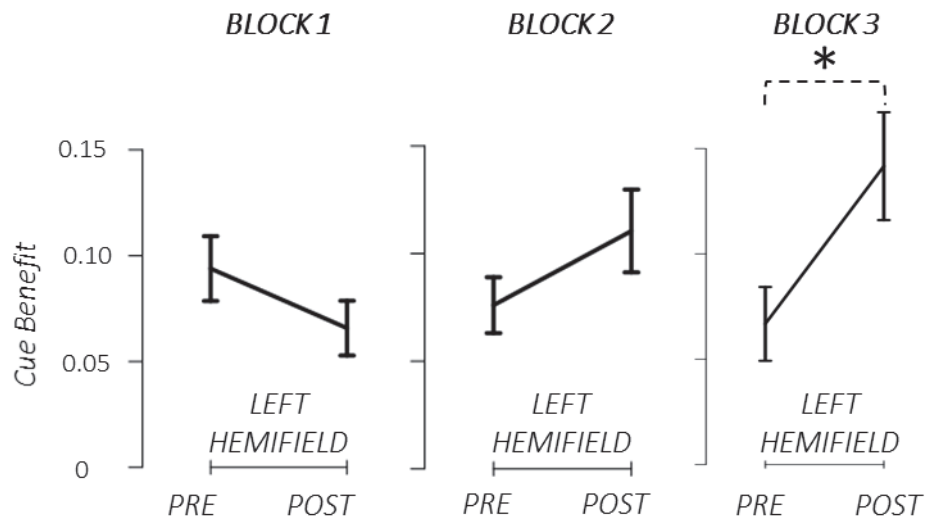


Figure 8: Pre- and Post-exposure results showing the progressive increase of cue benefit after backward adaptation exposure. Group mean (+/- SD) of cue benefit of left target after backward adaptation exposure.

The 2-factor rmANOVA (Hemifield x Phase) on the control data revealed a significant phase effect (partial $\eta^2 = 0.22$; $F_{(1,17)} = 4.75$; $p = 0.04$), showing a decrease of the cue benefit after the control exposure. The Hemifield effect and the interaction Hemifield x Phase effect were not significant (Figure 7, right panel).

The 2-factor rmANOVA (Eccentricity x Phase) on left hemifield data from the third block of backward exposure revealed a significant main effect of Phase (partial $\eta^2 = 0.22$; $F_{(1,17)} = 4.82$; $p = 0.04$) but no significant main effect of Eccentricity (partial $\eta^2 = 0.06$; $F_{(3,51)} = 1.16$; $p = 0.33$), nor any significant interaction between Phase and Eccentricity (partial $\eta^2 = 0.07$; $F_{(3,51)} = 1.22$; $p = 0.31$).

Concerning the link between the change in the left saccadic gain and the change in the cue benefit in the left hemifield, after backward adaptation (Figure in Supplementary), we did not highlight a significant correlation ($r_{(16)} = -1.52$; $p = 0.15$).

To summarize, these results show that on the one hand, the cue benefit decreased after a control exposure (mere execution of un-adapted saccades in both directions) but this decrease was not spatially specific as it was revealed in both hemifields (Figure 7 right panel). On the other hand, a specific increase of the cue benefit after backward adaptation of leftward saccades could be evidenced: this cue benefit progressively increased over the 3 blocks, reaching significance in Block 3, but only for target in the left hemifield (see Figure 8).

4. Discussion

The present study questioned the link between sensorimotor plasticity of the oculomotor system and visuospatial attention in healthy human subjects, thanks to a design testing the effect of adaptation of reactive saccades on exogenous orienting of attention. Pre- versus post- comparisons in the three exposure conditions of leftward saccades (backward adaptation, forward adaptation, control) highlight a boosting effect of exogenous attention specifically after backward adaptation, developing over time and affecting only the (left) adapted hemifield. The lack of significant correlation between the adaptation rate and the cue benefit boost suggests an all-or-none effect. These results both support the hypothesis of a coupling between SA and covert attention and confirm the difference between backward and forward adaptation mechanisms.

Our study provides the first demonstration of a coupling between SA and covert exogenous attention specifically after backward adaptation of leftward reactive saccades (RS). The only previous study of the effect of SA on detection performances, we are aware of, disclosed a boosting effect of backward SA but did not address the potential effect of forward SA (Habchi et al., 2015a). Instead this previous study reported a specificity related to RS, as this adaptation-related increase of detection performance was absent when voluntary saccades (VS) were adapted. This specificity was interpreted in the framework of segregated parieto-frontal systems involved in exogenous and endogenous attention (Corbetta & Shulman, 2002) with a partial overlap with the cortical substrates of adaptation mechanisms for, respectively, RS and VS (Gerardin et al., 2012). However as mentioned in Introduction, the significant effect of adaptation of leftward RS on visual detection performance disclosed by Habchi et al. (2015) could not be reproduced in our previous MEG study (Nicolas et al., 2018). As discussed in this last paper, the visual detection task used in these two previous studies might not have been sensitive enough to reliably disclose such a subtle behavioural effect of SA, despite being able to evoke measurable changes of electrophysiological activity in an extended cortical network including the parietal cortex. Accordingly, the detection task of the present study was designed to more robustly and specifically induce covert orienting of exogenous attention and to circumvent the limits of the speeded discrimination paradigm employed in these two studies. Indeed, attention relates to three systems: the alerting system, the executive system, and the orienting system (Posner & Petersen, 1990; Petersen & Posner, 2012). In the speeded discrimination paradigm, the orienting system was not manipulated. Therefore, it was not possible to disentangle whether the accelerated RT was due to a boost of alertness, of attention orientating, of motor preparation, or of decision making. In the present study, we therefore designed a Posner-like paradigm to specifically assess orienting of attention, and we used a peripheral cue with a short SOA to specifically measure exogenous orienting of attention. Moreover, our prediction

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concerned the benefit of attention, therefore we only presented informative cues (100% valid, no invalid) and uninformative cues (cue benefit). Analyses of the pre-exposure phase detection data revealed a significant cue benefit which did not depend on the three exposure conditions, providing a reliable baseline measure of exogenous attention orienting. Thus, the increase of cue benefit after backward adaptation of leftward RS not only confirms Habchi et al. 's (2015) original findings but solidifies their interpretation of a SA-related change of covert exogenous attention orienting processes. Strikingly, both studies report that the detection boosting effect is observed after backward adaptation of leftward reactive saccades. In addition, both showed this boosting effect to occur specifically for targets presented in the left hemifield, without any significant effect of target eccentricity within this adapted hemifield. Habchi et al. (2015) discussed their results in the framework of a boost of exogenous orienting of attention (although their design did not actually manipulate orienting of attention) and interpreted this effect as resulting from the known dominance of the right hemisphere for attentional processes. Here, our design brings evidence for a boost of genuine exogenous orienting of attention and further supports the asymmetrical attentional network as responsible for the hemispheric specificity of the effect.

Another study from our lab (Nicolas et al., under review) has investigated the effect of SA on visuospatial attention. In this study, we elicited backward adaptation of voluntary saccades separately in each hemifield, and tested the endogenous orienting of attention using a Posner-like paradigm. The results showed that after adaptation of leftward (and not rightward) VS, the endogenous orienting of attention assessed by the cue benefit was boosted for targets in both hemifields. This finding echoes the one reported here. Indeed, although addressing different saccade and attention modalities, both studies showed that adaptation of leftward saccades leads to an increase of cue benefit.

The present study brought up several new findings. First, the increase of cue benefit appeared during the 2nd block of the detection task and reached significance in the 3^d block. This suggests a slow time-course of the SA-related boosting effect on covert attention orienting. However, since we also highlighted that after control exposure, the cue benefit decreases, likely due to some fatigue effect, it sounds reasonable to propose that the boosting effect produced by backward adaptation needs first to counteract this fatigue effect and finally boost the cue benefit. Second, another original finding of the present study is the failure to elicit any change of covert attention following forward adaptation. The contrast between this negative finding and the positive effect after backward adaptation points toward distinct processes underlying forward SA versus backward SA, adding to an already long list of experimental evidence (e.g. Panouilleres et al., 2009; Panouillères et al., 2012; Schnier & Lappe, 2012) reviewed in Pélisson, Alahyane, Panouillères, & Tilikete, 2010). On the other hand, this lack of effect on

exogenous attention apparently contradicts the fact that forward SA is believed to rely on target remapping in cortical areas, as opposed to backward adaptation believed to result from alteration of the saccade trajectory control mechanisms at subcortical levels. This hypothesis has first been proposed by Semmlow, Gauthier, & Vercher, 1989 based on the pattern of spatial generalization of forward adaptation to un-adapted locations in the visual field. The lack of change of kinematic parameters of saccades after forward adaptation, relative to non-adapted saccades of matched amplitude, has also been used to support this hypothesis (Ethier, Zee, & Shadmehr, 2008). Finally, contrary to backward adaptation, forward adaptation has been shown to transfer to behavioral tasks which supposedly rely on cerebral cortical areas: visually-guided hand pointing movements performed in absence of eye movements (Hernandez, Levitan, Banks, & Schor, 2008), subjective localization responses of flashed targets under ocular fixation condition (Moidell & Bedell, 1988; Zimmermann & Lappe, 2010). Note however that, beside a contribution of the cerebellum (Golla et al., 2007; Panouillères et al., 2012; Panouillères, Miall, & Jenkinson, 2015), the neural substrates of forward adaptation in humans are completely unknown and remain to be determined through neuroimaging and/or neurostimulation studies. The above discussion and the present findings together predict that cerebral cortex areas would be recruited by forward saccadic adaptation, and that this cortical network would overlap with cortical systems involved in target spatial encoding but not with systems involved in exogenous orienting of attention. Concerning now backward adaptation, our positive findings lead us to suggest that the anatomical overlap of the cortical substrates of reactive saccades adaptation and covert exogenous attention described at the macroscopic level (see Introduction) would consist of common neuronal population co-activated for both processes. The hypothesis of an increased brain excitability by backward adaptation is consistent with our recent MEG study (Nicolas et al., 2018) demonstrating a power increase in the gamma oscillatory band which involved an extended cortical network including the ventral attention system, and which additionally persisted during a detection task performed just after the backward adaptation exposure. Given that gamma oscillations power is known to increase in relation to the efficiency of sensory processing (e.g. Womelsdorf, Fries, Mitra, & Desimone, 2006; Hoogenboom, Schoffelen, Oostenveld, & Fries, 2010; Tallon-Baudry & Bertrand, 1999) this pattern of modulation, found by Nicolas et al. (2018), might contribute to the functional coupling between backward adaptation of RS and covert exogenous attention. Moreover, the role of the PPC in spatial representation in interaction with visuospatial attention has also been highlighted using prism adaptation (PA). Indeed, (Pisella et al., 2005) proposed that PA relies on the cerebellum and affects cognition for patients with neglect.

Previous studies have used saccadic adaptation as a tool to investigate the coupling between pre-saccadic shift of attention and saccadic eye movements. The pre-saccadic shift of attention

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automatically unfolds to the saccade target just before saccade initiation (Deubel & Schneider, 1996), and thus departs from the purely covert shifts of attention investigated in the present study. By changing the saccade metrics in response to a given visual input, saccadic adaptation has been used to demonstrate that the pre-saccadic shift attention remained coupled with the endpoint of the (adapted) saccade, not to the visual target eliciting it (Doré-Mazars & Collins, 2005; Collins & Doré-Mazars, 2006; Collins, 2010; but see Ditterich, Eggert, & Straube, 2000). However, these previous findings refer to an oculomotor plasticity-visuospatial attentional phenomenon which differs from the one we have disclosed in the present study. First, attention orienting in our study was unrelated to any execution of saccades or even to any oculomotor preparation, as subjects kept central fixation throughout the entire detection tasks. Second, it was not related to the location corresponding to the adapted saccade endpoint (11°) as the effect was found for the entire range of tested eccentricities in the left hemifield (from 3° to 15°). This finding is consistent with the existence of broad adaptation fields which characterize the transfer of adaptation of a single saccade vector to other saccades (Pélisson et al., 2010). Indeed, although not measured in the present study, the adaptation field is likely to be broad enough to include all target locations used in the detection task. To check this proposal, one could try to spatially dissociate the adapted saccade vector and the vectors of target locations used in the detection task (increasing the difference of eccentricity and/or orientation).

Other studies have also indirectly supported the existence of a coupling between saccadic adaptation and other types of attention shifts. Saccadic adaptation can be induced solely by a perceptual target (Schutz, Kerzel, & Souto, 2014) or by a salient visual distractor attracting exogenous attention (Khan, McFadden, Harwood, & Wallman, 2014) both flashed in the vicinity of a stationary saccade target. McFadden, Khan, and Wallman (2002) showed that it is possible to adapt the exogenous shift of attention by 'stepping the attentional target' during a covert attentional task (eye movements not allowed), and that this procedure resulted in a change in saccade amplitude. Another study demonstrated that saccadic adaptation efficiency increases with attentional load (Gerardin et al., 2015). These four studies thus suggest that modifications of visuospatial attention can impact saccadic adaptation.

5. Conclusions

Taken together, these present findings highlight a functional coupling between saccadic adaptation and visuospatial attention. This coupling could be subtended by shared neuronal substrates at the level of the PPC. Our results further support the contribution of the motor system in the attention system and lead towards promising rehabilitation procedure for patients with visuospatial disorders.

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2.2. Supplement

Supplementary methods

Power analysis. The number of subjects was determined from the following power analysis performed through the G*Power software (Faul et al. 2007). As stated in Introduction, we are aware of only one previous study testing the coupling between SA and visuospatial attention (Habchi et al., 2015). This study disclosed that after adaptation of RS in the left hemifield, the performance in a visual detection task improved in the left hemifield. This was revealed by a significant 3-level interaction in a repeated measures ANOVA (rmANOVA) with subjects as the repeated measure, the target hemifield (left or right), the phase (pre- or post-exposure) and the exposure (leftward adaptation, rightward adaptation, or control) as within-factors. We have computed the effect size of this interaction and found a value of 0.41 (Sum of Square of the numerator = 485.7; Sum of Square of the denominator = 695.8), resulting in an achieved power larger than 99% according to the G*Power software. However, since the present study will address another modality (*i.e.* voluntary saccades and endogenous attention), we decided to reduce this effect size to a conservative level of 0.2.

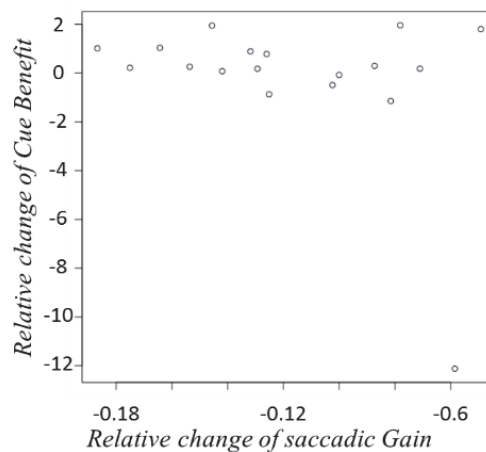
Given this medium effect size ($f = 0.2$), we found that 14 subjects are required for our interaction of interest between the 3 within-subjects to reach a power of 95.3% when assuming an average correlation coefficient of $r = 0.85$ between repeated measures and a nonsphericity correction of $\epsilon=0.5$ (see below). To counterbalance the six possible testing orders in the sessions included in our design, we decided to increase for each experiment this number up to 18 subjects, reaching a power of 98.9%.

The power analysis is also based on a pilot study we performed to find the best Stimulus Onset Asynchrony for our endogenous task. The SOA, the duration between the cue appearance and the target appearance, is the time allocated to endogenous attention to shift and develop. Our pilot study consisted in testing the attention task described in the main text (see Attention task: visual discrimination in the section Apparatus, stimuli and procedure of the MATERIALS AND METHODS) for 3 different SOA (602 ms / 850 ms and 1106 ms), each SOA condition being evaluated in a separate session comprising 3 blocks of 52 trials. These pilot data (RT of discrimination response) allowed us to establish a main effect of cue type regardless of the SOA duration (effect size = 0.88; $F(1,3) = 22.3384$; p -value = 0.0179). No main effect of SOA nor interaction between SOA and cue type was significant. They also allowed us, using the Mauchly's test for sphericity, to check that the sphericity of the 3-level factor SOA is respected ($W=0.27$; p -value = 0.279). Finally, these data allowed us to determine the correlation between repeated measures: the correlation of discrimination RT between the three SOA conditions (602 ms *versus* 850 ms, 602 ms *versus* 1106 ms, and 850 *versus* 1106 ms), using Pearson's product moment correlation coefficient tests, turned out to be highly significant in all three cases (p -values < 10^{-5} and r -values > 0.85). We therefore set the correlation between repeated measures at $r=0.85$.

Instructions and feedback. Before the experiment started, the experimenter first displayed on the screen the two types of trials (informative and uninformative) and informed subjects about the presence of 'No-Go' trials. Then, the experimenter displayed instructions on how feedback about their detection performances will be provided after each block of trials, namely by means of a gauge filling up or down depending on subject's performance (translated from French: "if you use the cue well enough to be fast, the gauge will fill up otherwise it will empty. The gauge will also empty if you answered to too many 'No-Go' trials."). At the beginning of each session, this 10 graduations gauge was initially filled to the

fourth graduation. At the end of each block the gauge was presented filled up to a new graduation according to the subjects' score during the block: one graduation was gained if they were faster in informative trials than in uninformative trials, and two graduations were gained when the subjects additionally did not answer to more than 2 'No-Go' trials. Conversely, one graduation was lost if subjects' median performance was slower in informative trials than in uninformative trials. Increases or decreases of gauge levels were emphasized by a green or red filling color, respectively. In addition, each possible change of gauge level was accompanied by the following sentences: "Be careful, you need to better use the cue" (one graduation down), "Good, but you can still better use the cue" (one graduation up); "Bravo, keep on using the cue this way!" (two graduations up). Finally, a sentence was displayed requesting the subject to signal when she/he was ready to start the next block. These written feedbacks and instructions are intended to avoid non-standardized oral feedback from the experimenter who could not be blind regarding the type of session (backward, forward, or control exposure conditions).

Supplementary results



3. Study 3: Effect of VS adaptation on endogenous orienting of attention

3.1. Main article

Title: “Inducing oculomotor plasticity to disclose a functional link between voluntary saccades and endogenous attention deployed peripherally”

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ABSTRACT

To what extent oculomotor and attention systems are linked remains strongly debated. Previous studies suggested that saccadic adaptation, a well-studied model of oculomotor plasticity, and orienting of attention rely on overlapping networks in the parietal cortex and can functionally interact. Using a Posner-like paradigm in healthy human subjects, we demonstrate for the first time that saccadic adaptation boosts endogenous attention orienting. Indeed, the discrimination of peripheral targets benefits more from central cues after backward adaptation of leftward voluntary saccades than after a control saccade task. We propose that the overlap of underlying neural networks actually consists of neuronal populations co-activated by both oculomotor plasticity and endogenous attention. The functional coupling demonstrated here plaid for conceptual models not belonging to the framework of the premotor theory of attention as the latter has been rejected precisely for this voluntary/endogenous modality. These results also open new perspective for rehabilitation of visuo-attentional deficits.

KEYWORDS

Oculomotor plasticity, Visuospatial attention; Endogenous orienting; Voluntary saccades

1. Introduction

As much as we would like to, our brain is not able to deal with the huge amount of information brought up by our senses. Especially when it comes to vision, albeit the dominant sense of primates, our brain resources are too limited to efficiently handle visual information sensed by the millions of photoreceptors of our eyes. Therefore, we need to select what part of space we want to pay attention to. Visuospatial attention is a cognitive process which plays a critical role in this selection by facilitating the visual processing of objects and features falling in the area of space where it is focused on, at the expense of those situated outside (Posner, 1980; Carrasco et al., 2000). To get a refined and homogenous analysis of our entire visual field, this attentional focus must be frequently re-oriented either automatically, in response to the sudden appearance of a stimulus (exogenous attention) or voluntarily, being driven by internal goals (endogenous attention) (Posner, 1980). These two attention-shifting mechanisms are partially distinct, relying respectively on the ventral and dorsal streams of attention (Corbetta and Shulman, 2002; Corbetta et al., 2008), and both can either or not be accompanied by eye movements (overt and covert shifts, respectively).

Saccadic eye movements are also of utmost importance to explore our visual environment and select meaningful information therein. Indeed, as visual acuity is highest in the narrow central zone of the visual field processed by the fovea, gaze shifts are mandatory to explore a visual scene. Like attention shifts, gaze shifts are either exogenously or endogenously triggered, corresponding to so-called reactive (RS) or voluntary saccades (VS), respectively. Shifts of attention and saccadic eye movements share several other features, up to the point that, in the framework of the premotor theory of attention, attention shifts are considered to be unexecuted saccades inhibited at the oculomotor output level (Rizzolatti et al., 1987).

Saccadic adaptation (SA) is a well-studied sensorimotor adaptation process (see for reviews Hopp and Fuchs, 2004; Pélisson et al., 2010) and therefore constitutes a convenient tool to assess the role of the oculomotor system on spatial attention. Interestingly, the neural substrates of SA and of visuospatial attention overlap. Indeed, the intraparietal sulcus (IPS) has been involved in both adaptation of VS (Gerardin et al., 2012; Panouillères et al., 2014) and endogenous attention (see for review Corbetta and Shulman, 2002) while the right temporo-parietal-junction (rTPJ) has been involved in adaptation of RS (Gerardin et al., 2012; Pélisson et al., 2018; Nicolas et al., 2018; Guillaume et al., 2018) and exogenous attention (Corbetta and Shulman, 2002). Moreover, two behavioral studies have suggested that this overlap might have functional consequences: the first reports increased performances in a visual detection task performed after adaptation of RS (Habchi et al., 2015), and conversely, the second shows that RS adaptation efficiency is increased when subjects are simultaneously engaged in an attention-demanding task directed to the saccade target (Gerardin et al., 2015). Note, however, that the visual detection task used by Habchi et al did not allow to specifically isolate covert attention shifts from the other cognitive or motor components involved. In addition, and to the best of our knowledge, the coupling between SA and attention has never been investigated in the endogenous modality. As the premotor theory of attention has been challenged for the voluntary/endogenous modality (see for review Smith and Schenk, 2012), highlighting a functional link between oculomotor plasticity and endogenous attention would have strong theoretical implications.

Therefore, the present study aimed at investigating the coupling between saccades and visuospatial attention in the endogenous modality, using a Posner-like paradigm allowing to specifically assess pure covert attention shifts before and after the development of voluntary saccades adaptation.

2. Materials & Methods

2.1. Subjects

The experiment adheres to the code of ethics of the World Medical Association – Declaration of Helsinki (2008) and received the approval of the Ethics Committee of INSERM (CEEI - IRB 00003888, n°16-305). Forty-one subjects provided a written informed consent before performing the tasks and received a compensation for their participation. Among those subjects, four were excluded because they did not show significant saccadic gain modulation in one of the two adaptation exposures and one was excluded because of poor discrimination performances (for details see 2.3.1.1 of the Saccadic tasks section and 2.3.2.1 Attention task). The remaining subjects were all right-handed except one, comprised 17 males and 19 females, with a mean age of 25.5 +/- 4.53 SD (Standard Deviation). Their vision was normal or corrected-to-normal. Criteria of exclusion were: neurological or psychiatric disorders history; cognitive disorders preventing the comprehension of the instructions; severe sleep deprivation during the last 24 hours; consumption of psychotropic drugs, substances, or alcohol during the last 24 hours; participation to other experiments involving sensorimotor adaptation during the last week. After written consents obtained, each subject was assigned pseudo-randomly to one of the six sub-groups of each experiment, corresponding to the 6 possible orders of testing in the three sessions (within-subject design, see General design section). The number of subjects was determined from a power analysis performed through the G*Power software (Faul et al., 2007) and based on parameters established from the literature and from pilot data (see Power analysis in the Supplementary Methods).

2.2. Apparatus, stimuli, and procedure

2.2.1. Apparatus

Experiments were carried out in a dimly lit room. Subjects were installed in a comfortable position with the head stabilized by a chin-rest, cheekbone rests, and forehead support; they faced a computer screen (1920 x 1080 pixels; 53.5 x 34.5 cm; 144 Hz refresh rate) at 57 cm from their eyes. Experiments are timed based on the 144 Hz refresh rate of the computer display (frame duration approximately 7 ms), therefore all time-intervals reported in the following represent multiple of the frame duration and are rounded to the nearest value in milliseconds. Psychopy (Peirce, 2008), an open-source software, was used for the stimuli presentation and data collection in all different tasks. Movements of the right eye were recorded at a frequency of 1000 Hz using the remote configuration of the EyeLink 1000 infrared eye-tracker (SR research, Canada). Each task started with the calibration of the eye-tracker by asking subjects to fixate a series of 5 targets displayed near the borders and at the center of the screen.

2.2.2. General design

Experiments 1 and 2 were carried out separately in two different experimental groups. The two experiments were identical except for the eccentricity of the target in the attention task (see Attention task : visual discrimination in the Apparatus, stimuli, and procedure section). In each experiment, subjects were submitted to three experimental sessions (within-subjects design), each of which ('leftward adaptation', 'rightward adaptation' and 'control') comprising identical pre-exposure and post-exposure phases as well as a specific exposure phase (Figure 1). During all three exposures, saccades in both directions were performed. In the leftward adaptation, only leftward saccades were adapted; conversely in the rightward adaptation, only rightward saccades were adapted; finally in the control, no saccades were adapted. This control session allowed assessment of unspecific effects of exposure to a saccadic task. The effects on attention were measured by comparing, between the pre- and post-exposure phases of each session, subjects' performance in a visual discrimination attention task; in addition, comparing the gain of saccades measured during a test saccade task performed before and after exposure allowed us to check for successful saccadic adaptation in the respective hemifields. The delay between each session was at least 14 days in order to avoid any retention of saccadic adaptation between sessions, based on a previous study disclosing a significant retention of adaptation up to 5 days after exposure but not 11 days after (Alahyane and Pélisson, 2005).

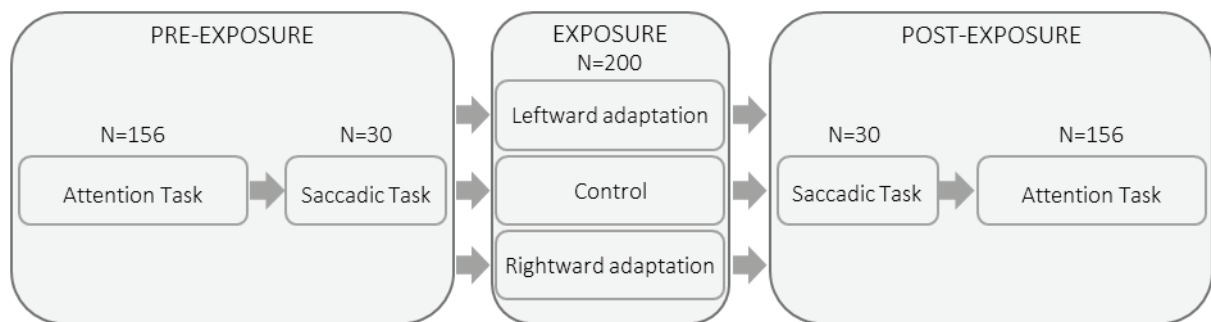


Figure 1: Study general design. In both Experiments 1 and 2, each subject underwent 3 experimental sessions -composed of a pre-exposure, an exposure and a post-exposure phases - differing only by the exposure phase (either leftward adaptation, rightward adaptation or control). N = number of trials.

2.2.3. Saccadic task

The saccadic adaptation was performed by a modified version of the double-step paradigm introduced by McLaughlin (1967). This paradigm consists in displacing the visual scene while the subject is executing a saccade towards a peripheral target. Thanks to the saccadic suppression phenomenon, this intra-saccadic visual displacement is usually not consciously perceived by subjects and leads to a mismatch between post-saccadic eye fixation and target location which is interpreted by the central nervous system as a saccade aiming error.

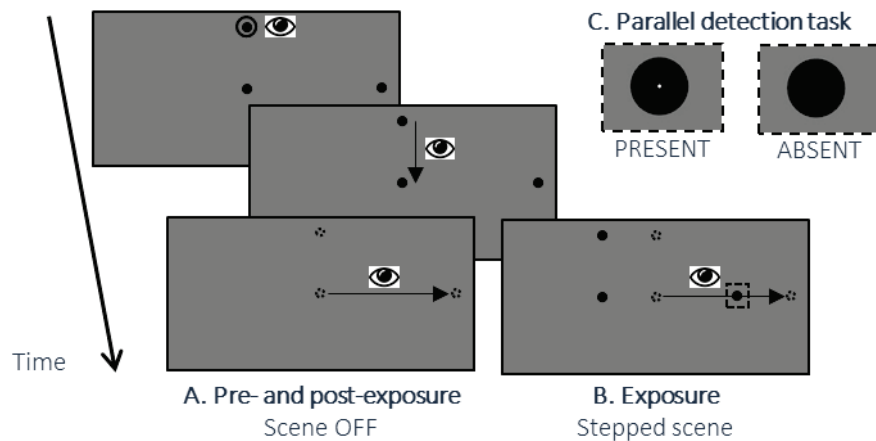


Figure 2: Time-line of a trial in the saccadic tasks (not to scale). After the circle around the fixation point turns off, subjects had to make, at their own pace, a downward saccade to the central point and then a horizontal –voluntary– saccade to the peripheral target. A. In the pre- and post-saccadic phases, the visual scene was turned off as soon as the voluntary saccade was detected. Subjects were instructed to keep looking at the peripheral target position for ~ 1 sec and then look back to the upper location in anticipation of the fixation point re-appearance, using that time period to blink if necessary. B. In the exposure phase, the visual scene was shifted backward immediately at the voluntary saccade onset (adapted saccades) or after 805 ms (unadapted saccades). The scene remained for 1610 ms in total in both conditions. The size of the shift increased progressively across blocks 1-4 (respectively 1°, 2°, 3° and 3°). C. Enlarged view of peripheral targets during the exposure phase: subjects additionally performed a simple detection task to favor a sustained motivation: they had to report by a push button the presence of a small white dot inside the peripheral target (visible only in perifoveal vision after the saccadic response: see enlarged views of a dot-present target and of a dot-absent target). Feedback regarding this simple detection task was given at the end of each block.

Sequence of events for adapted saccade trials (Figure 2B).

Three dots of 0.3° of visual angle were displayed on the computer screen. The first dot was located 4° above the center of the screen, and was surrounded by a small circle. The second dot was at the center of the screen. The third dot, the peripheral target, was at 9° of eccentricity aligned with the horizontal meridian, either to the left or to the right. The side of the peripheral target was blocked with 12 trials in the adapted direction, 12 in the opposite direction, repeated 2 times for each block. The subject had to fixate the upper dot during a pseudo randomized delay between 301 ms and 701 ms after which the disappearance of the surrounding circle ('go signal') indicates that he/she had to look successively at the other two targets. Correct eye fixation of the upper dot was ensured by continuous monitoring of the eye-tracker signal. In the next 2000 ms, the subject had to make at her/his own pace, a first saccade towards the central dot (vertical saccade) and then a second saccade from there towards the peripheral target (horizontal voluntary saccade). The voluntary saccade was detected when the eye velocity was higher than 70°/s (Dalmajer et al., 2014). This event immediately triggered the shift of the visual scene when the peripheral target was in the adapted hemifield (Figure 2B). The visual scene shift was progressively increased through the blocks (1° for the first block, 2° for the second, 3° for the third and fourth blocks) leading to a progressive decrease of the target final eccentricity (8°, 7° and 6° respectively). The visual scene remained visible for a total of 1610 ms after the detection of the voluntary saccade. The subject then had a delay of 1000 ms to blink and look back to the upper dot. The next trial started as soon as correct fixation of the upper dot location was detected.

Sequence of events for unadapted saccade trials.

These trials were identical to the adapted saccade trials except that the jump of the visual scene occurred 805 ms after the detection of the voluntary saccade. These trials correspond to the saccades toward the unadapted hemifield for the leftward and rightward exposure and for the saccades toward both hemifields in the control exposure.

The total exposure phase consisted of 196 trials distributed in 4 blocks of 48 trials each (24 with a right target and 24 with a left target). Between each block, the subject was allowed to rest with the head still as long as needed.

To maximize subjects' involvement and motivation throughout the saccadic tasks, they were requested to perform in parallel an easy detection task: in random trials (from 5 to 20 per block), the peripheral target contained a white dot of 0.008° of visual angle (not detectable in peripheral vision but easy to detect after the saccade to the target), and subjects had to push a button after each trial in which they detected the white dot. Performance feedback was provided to subjects during the rest period between the blocks but was not further analyzed.

Pre- and post-exposure saccadic tasks (Figure 2A).

These tasks were identical to the exposure tasks except that the visual scene did not jump but instead was turned off at the initiation of the voluntary saccade. Each task consisted in one block of 30 trials (15 with a right target and 15 with a left target, randomly ordered). Comparison between pre- and post-exposure tasks allowed determination of the SA after-effect (change of saccade amplitude in post-versus pre-exposure) and thus quantitative assessment of the adaptation strength.

2.2.4. Attention task : visual discrimination

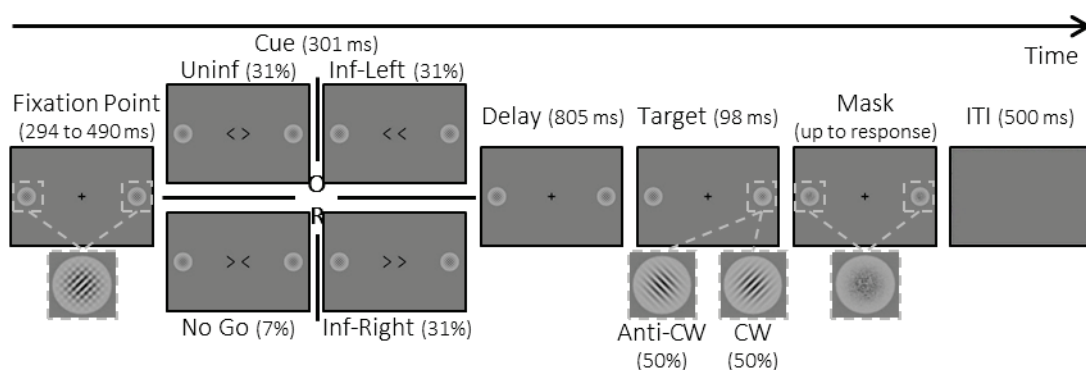


Figure 3: Time-line of a trial in the attention task. A central fixation cross and 2 lateral placeholders (eccentricity: 7.5° in Experiment 1; 3° in Experiment 2) each containing 2 orthogonal gratings, were present at the beginning of the trial. Then central cues appeared for 301 ms, either indicating the side of the upcoming target (100% valid informative cue: Inf-Left or Inf-Right), or providing no spatial information (uninformative cue: Uninf), or indicating to restrain the response (No Go cue). The target presented after 805 ms of delay (SOA = 1106 ms) consists in the brief disappearance of one grating on one side (left 50% or right 50%), followed after 91 ms by a mask. Using a push / pull device, subjects had to respond as fast and as accurately as possible whether the target was tilted clockwise (CW) or anti-clockwise (anti-CW). Experiments 1 and 2 differed only according to the eccentricity of the discrimination target and associated place-holder.

A variant of the Posner task (Posner, 1980) was designed with the main features (a central cue, and a long SOA) chosen to evoke shifts of endogenous attention. Contrasting between informative trials (cue always valid) and uninformative trials (uninformative cue) allowed us to measure the pure benefit of endogenous attention orienting. This approach was preferred over that used in many endogenous attentional studies, consisting of contrasting between valid and invalid cues, which rather yields the cumulated effect of exogenous costs and endogenous benefits (Chica et al., 2013; Chica et al., 2014).

Sequence of events in the attention task trials (Figure 3).

A fixation cross subtending 1° of visual angle appeared at the center of the screen (grey 50%) at the beginning of the trial and, except during the cue period, remained visible until the subject's response. Subjects had to keep eye fixation on that location all throughout the trial. Two light grey (35%) placeholders (circles of 2.5° of visual angle in Experiment 1; 1.5° in Experiment 2) were also presented along the horizontal meridian, on the left and on the right, at 7.5° of eccentricity in Experiment 1, and at 3° of eccentricity in Experiment 2. Each placeholder initially contained two gabor patches (Experiment 1: 4 cycles per degree (cpd) of spatial frequency and 2.5° of visual angle; Experiment 2: 4 cpd of spatial frequency and 1.5° of visual angle) presented with a Gaussian mask and superimposed orthogonally (one gabor tilted at 45° and the other at -45° relative to the vertical, leading to the perception of a grid). The contrast of the gabor patches was previously determined for each individual by a staircase procedure to achieve a 80% level of correct discrimination (see Staircase procedure in Supplementary methods). After a pseudo-randomized (294 to 490 ms) delay from the beginning of the trial, a cue appeared for 301 ms. This cue was composed of two empty arrows (1.5° vertically x 1° horizontally) flanking the center of the screen (1.0° of horizontal spacing). For \sim two thirds of the trials (32 'informative trials' out of 52 trials for each block) the cue validly informed the future target location: the two arrows both pointed either toward the left or toward the right of the screen to indicate the placeholder in which the target will appear. In 16 'uninformative' trials (\sim one third), the cue did not provide any spatial information about the upcoming target, the two arrows pointing outwards. The 1:2 ratio of uninformative versus informative trials was meant to potentiate the cueing effect (Bidet-Caulet et al., 2015). In the four remaining trials of each block, a 'no-go cue' represented by the two arrows pointing inwards instructed subjects to refrain from answering. These 'no-go' trials were meant to enforce subjects to use the cue to perform the task correctly, and thus favoring the conscious interpretation and increasing the benefit of the cue. However, they were not analyzed. In all trials, the cue period was followed first by displaying again the fixation point and then 805 ms after cue offset by a brief extinction (98 ms) of one of the two gabor patches either in the left placeholder (50%) and or in the right placeholder (50%): the remaining gabor patch thus constitutes the target (SOA = 1106 ms) which orientation had to be discriminated. Immediately after this target presentation, a mask was displayed in the two placeholders until the subject's response was made or for a maximum duration of 1500 ms. Subjects had to discriminate as fast and as accurately as possible whether the target gabor patch was tilted clockwise or anticlockwise (45° or -45° with respect to the vertical, respectively). Subjects answered with their index finger through a double switch device oriented in their mid-sagittal axis, with a response assignment randomized between subjects: half of them pushed the switch for a "clockwise" target and pull it for an "anticlockwise" target, the other half was instructed with the opposite assignment. Eye fixation was continuously monitored all throughout the trial and whenever the subject broke fixation (gaze deviating in any direction more than 1.5° from the fixation cross), the fixation cross immediately turned red and the trial was aborted. Aborted trials were replayed back during the same block of trials. We chose a SOA duration of 1106 ms in order to minimize any

involvement of attention oriented exogenously (Ristic and Kingstone, 2012). Moreover, the pilot data reported in Supplementary data showed that the duration of the SOA does not affect the validity effect in our discrimination task.

The task consisted of 3 blocks of 52 trials each (156 in total): 16 'informative - left target' and 16 'informative - right target', 8 'uninformative - left target' and 8 'uninformative - right target', and 4 'no-go cue'. Between each block, subjects received standardized feedback about their performance (see Instructions and feedback in Supplementary methods).

2.3. Data analysis

Data analyses were performed with the open-source software R (The R Core Team, 2013). These analyses concerned the saccadic behavior during the pre- and post-exposure saccadic tasks as well as the performances in the attention tasks measured by cue benefit (relative change of reaction – RT – between informative and uninformative trials). Any exclusion of a subject due to criteria described in the following paragraphs led to his/her replacement. All the group analyses have been carried out separately for the two experiments.

2.3.1. Saccadic tasks

2.3.1.1. Preprocessing

Eye movement data were analyzed off-line using custom software developed in Matlab (Math Works Inc., Natick, MA, USA). The beginning of the primary horizontal saccade was identified offline based on a velocity threshold of 30°/s. Saccadic amplitude was measured as the difference between eye positions 50 ms before the saccade onset and 50 ms after the saccade offset. The gain of a saccade was used as the dependent variable in the saccadic tasks: it was computed as the ratio between saccadic amplitude and initial target eccentricity (difference between target position and starting position of the saccade). Saccades with a gain less than 0.5 or outside the mean $\pm 2SD$ interval were discarded from further analysis.

2.3.1.2. Statistical analysis

Since the saccadic adaptation was critical to test our hypothesis, we excluded from the main analysis subjects who did not show the expected decreased gain of saccades in the adapted hemifield. To this aim, we first performed, separately for each subject and each hemifield, a unilateral Student t-test comparing the gain of the saccades between the pre- and the post-saccadic tasks and used a threshold p-value of 0.05 after FDR (False Discovery Rate (Benjamini and Hochberg, 1995)) correction for 6 multiple comparisons. Moreover, for representational purposes, we computed the exposure after-effect for each hemifield and each exposure condition as follow:

$$\begin{aligned} \text{Exposure after - effect}_{\text{exposure of interest}} \\ = \frac{\text{mean gain}_{\text{post-exposure}} - \text{mean gain}_{\text{pre-exposure}}}{\text{mean gain}_{\text{pre-exposure}}} \end{aligned}$$

A negative exposure after-effect reflects a decrease of the saccadic gain between the pre- and the post-exposure phases.

Finally to calculate the effect size of the exposure after-effect in the exposure sessions, we computed the mean of the gain for each subject, in the adapted hemifield for the pre-exposure and the post-exposure phase separately. These values were used to calculate the Cohen's *d* effect size for Student *t* test.

2.3.2. Attention task

2.3.2.1. Preprocessing

To ensure that the level of involvement of each subject was high, subjects with low global performance or with high fluctuations were excluded. To this aim, each session were divided in 8 experimental cells of conditions (2 cue types x 2 target hemifields x 2 phases, smallest cell = 24 trials). We excluded subjects with a number of correct trials inferior to 8 for any of these cells. Then, trials with outlier RT were excluded using the John Tukey's method of leveraging the Interquartile Range, and the median RT of the remaining trials was computed in each of these cells. If one cell's median RT lies outside ± 3 SD (Standard Deviation) from the subject's average of median RTs computed across the 8 cells, the subject was excluded.

2.3.2.2. Outcome neutral criteria

First of all, a significant difference of RT between the informative trials and uninformative trials in the pre-exposure phase was a prerequisite to demonstrate that, at the group level, our attention task readily engaged the orienting of endogenous attention. For that purpose, a 2-way rmANOVA was performed on RT of the pre-exposure phases only, with cue type as 2-level factor (informative / uninformative) and exposure as 3-level factor (control, leftward and rightward adaptation). The critical outcome neutral criterion was a main cue type effect and an absence of significant interaction between cue type and exposure factors, which would allow us to demonstrate a significant difference of RT during pre-exposure between informative trials and uninformative trials, irrespective of the exposure session.

2.3.2.3. Statistical analysis

For this analysis, the dependent variable was the subjects' cue benefit on discrimination RT, which was computed as follows:

$$\text{Cue benefit}_{\text{exposure of interest}} = \frac{RT_{\text{Uninformative}} - RT_{\text{Informative}}}{RT_{\text{Informative}}}$$

This dependent variable was averaged in each of the 12 experimental cells defined from the factors of the following rmANOVA, and then submitted to this rmANOVA, with subjects as the repeated measure, the target hemifield (left or right), the phase (pre- or post-exposure) and the exposure (leftward adaptation, rightward adaptation, or control) as within-factors.

Post Hoc analyses of significant interaction was performed using paired Student t-tests separately for each of the three exposure conditions. The three p-values were then FDR corrected.

Finally, after highlighting an effect after leftward adaptation on cue benefit in both hemifields in Experiment 2 (see Results), we sought for a correlation (Pearson's product-moment correlation) between the after-effect of leftward saccades adaptation (see formulae above) and the relative change of cue benefit between the pre- and the post-exposure of leftward adaptation, calculated as follow:

$$Relative\ Change_{Cue\ benefit} = \frac{Cue\ benefit_{post-exposure} - Cue\ benefit_{pre-exposure}}{Cue\ benefit_{pre-exposure}}$$

3. Results

3.1. Pre- and post-exposure saccadic tasks

After rejection of subjects and trials following the above mentioned criteria (see Preprocessing in the Saccadic tasks section for details), the average number of analysed trials per condition was 13.6 +/- 1.3 SD in Experiment 1 and 12.4 +/-1.7 SD in Experiment 2. The mean saccadic gain in pre- and post-exposure, as well as the individual and mean adaptation after-effect, are illustrated in Figure 4. As it was a pre-requisit (see Subjects section), all subjects of each experiment showed in the adaptation sessions a significant decrease of the saccadic gain for target presented in the adapted hemifield, in the post-exposure as compared to the pre-exposure, thus having a significant after-effect due to SA (Figure 4, right panel). Moreover, as seen in Figure 4 (left panel), this decrease was not seen in the opposite, unadapted, hemifield, whether for the leftward or rightward exposure. In addition no gain change in either hemifield took place in the control exposure.

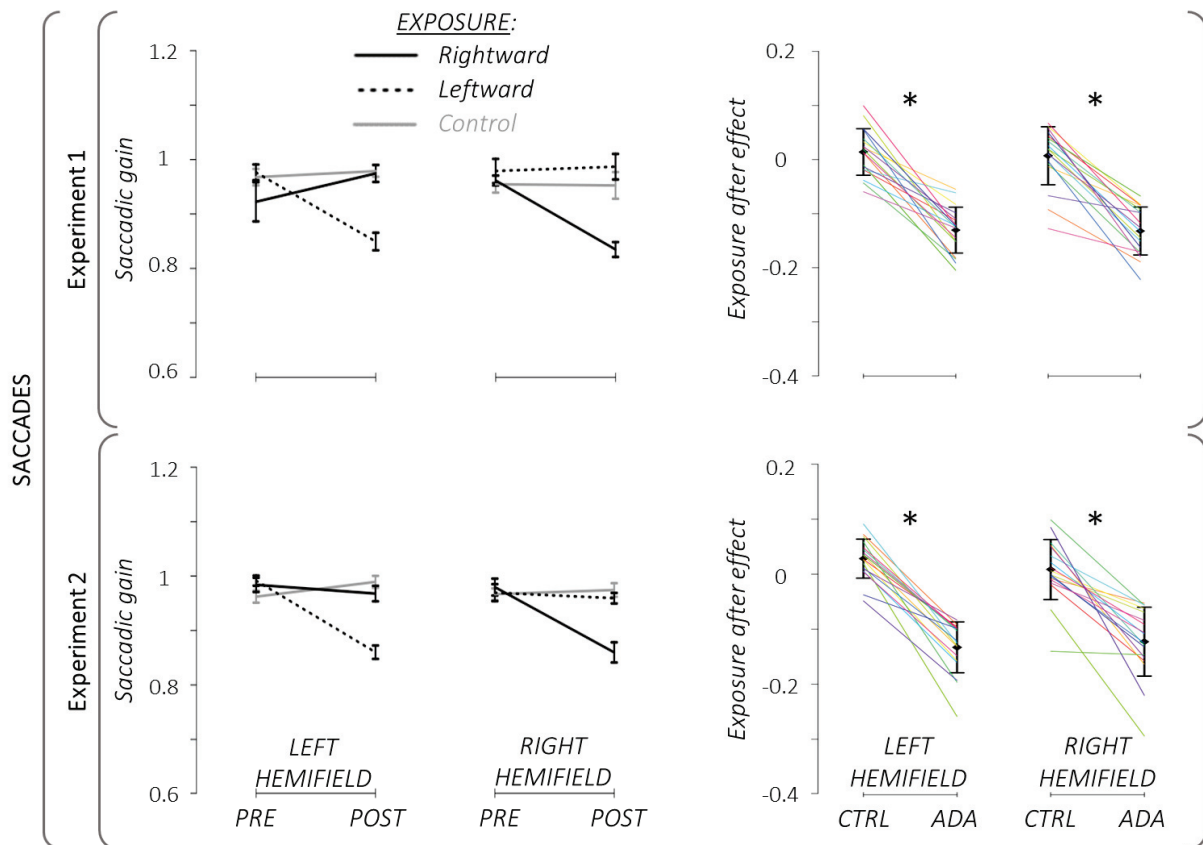


Figure 4: Pre- and Post-exposure saccadic task results. *Left:* Group mean (+/- SD) of saccadic gain for Experiment 1 (**upper panel**) and Experiment 2 (**lower panel**). Black lines: rightward adaptation exposure; Black dotted: leftward adaptation exposure; Grey lines: control exposure. **Right:** Individual percent gain changes between the pre- and the post-exposure tasks (**after-effect**) for Experiment 1 (**upper panel**) and for Experiment 2 (**lower panel**). Only data from the adapted hemifield are shown for adaptation exposures (ADA), i.e. left or right hemifield for adaptation exposure of leftward and rightward saccades, respectively; and values of the control exposure (CTRL) are plotted for each corresponding hemifield. Solid black lines represent group mean (+/- SD) and colored lines stand for individual values. *: p -value < 0.05

3.2. Attention task

3.2.1. Experiment 1 (target at 7.5°)

3.2.1.1. Outcome neutral criteria

After rejection of subjects and trials following the above mentioned criteria, the average number of analysed trials per condition was 58.9 +/- 5.6 SD (see Preprocessing in the Attention task section for details). The rmAnova of outcome neutral criteria on the pre-exposure RT revealed a significant main effect of the cue type (partial $\eta^2 = 0.81$; $F_{(1,17)} = 74.15$; $P = 1.32e^{-7}$; achieved power = 1; Figure 5, left panel). The main effect of the exposure was not significant (partial $\eta^2 = 0.01$; $F_{(2,34)} = 0.17$; $P = 0.85$), nor the interaction between exposure and cue type (partial $\eta^2 = 0.01$; $F_{(2,34)} = 0.28$; $P = 0.76$). Therefore, our attention task did engage the orienting of attention during the pre-exposure phase, and did so similarly in the three sessions.

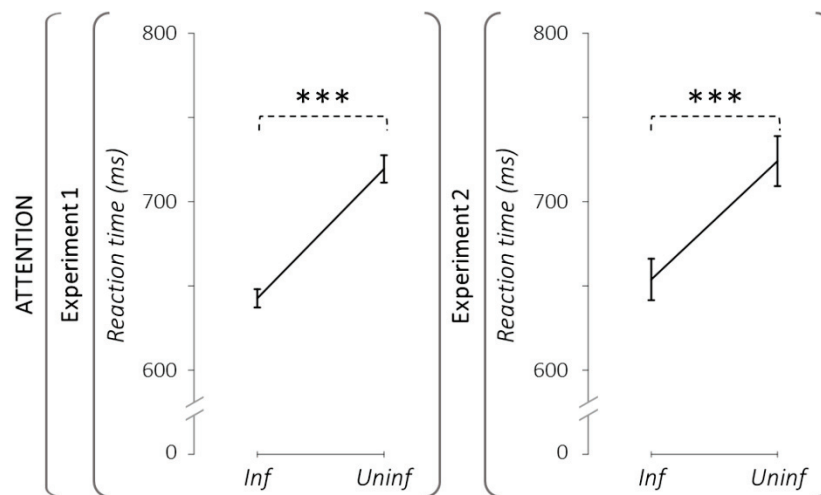


Figure 5: Effect of cue type on reaction time in the pre-exposure attention task. Group mean (+/- SD) of median reaction times (ms) in Experiment 1 (left panel) and in Experiment 2 (right panel). A general effect of cue type was disclosed by the decrease of RT for informative as compared to uninformative trials. ***: p -value < 0.001

3.2.1.2. Statistical analysis

The performance in the attention task was evaluated by computing the cue benefit of subjects' (Figure 6). Submitting cue benefit to a rmANOVA with the factors exposure x phase x target hemifield revealed no significant main effect and no significant double nor triple interaction (all $P > 0.32$). Therefore, no further analysis was performed. In summary, no significant effect of saccadic adaptation on attention performance could be revealed when the target was presented at 7.5° .

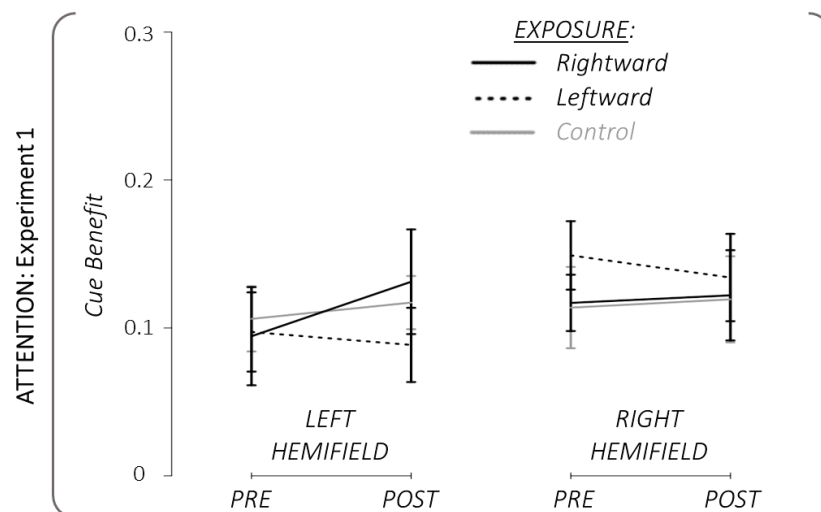


Figure 6: Pre- and Post-exposure attention results in Experiment 1. Group mean (+/- SD) of cue benefit for the pre- and the post-exposure phases in the two hemifields of target presentation. Black lines: rightward adaptation exposure; Black dotted lines: leftward adaptation exposure; Grey lines: control exposure.

3.2.2. Experiment 2 (target at 3°)

3.2.2.1. Outcome neutral criteria

After rejection of subjects and trials following the above mentioned criteria, the average number of analysed trials per condition was 57.0 +/- 7.4 SD (see Preprocessing in the Attention task section for details). The rmAnova of outcome neutral criteria on the pre-exposure RT revealed a significant main effect of the cue type (partial $\eta^2 = 0.64$; $F_{(1,17)} = 30.81$; $P = 3.52e^{-5}$; achieved power = 1; Figure 5, right panel). The main effect of the exposure was not significant (partial $\eta^2 = 0.03$; $F_{(2,34)} = 0.44$; $P = 0.65$), nor the interaction between exposure and cue type (partial $\eta^2 = 0.05$; $F_{(2,34)} = 0.81$; $P = 0.45$). Thus, as for Experiment 1, the attention task in Experiment 2 engaged the orienting of attention during the pre-exposure phase, and did so similarly in the three sessions.

3.2.2.2. Statistical analysis

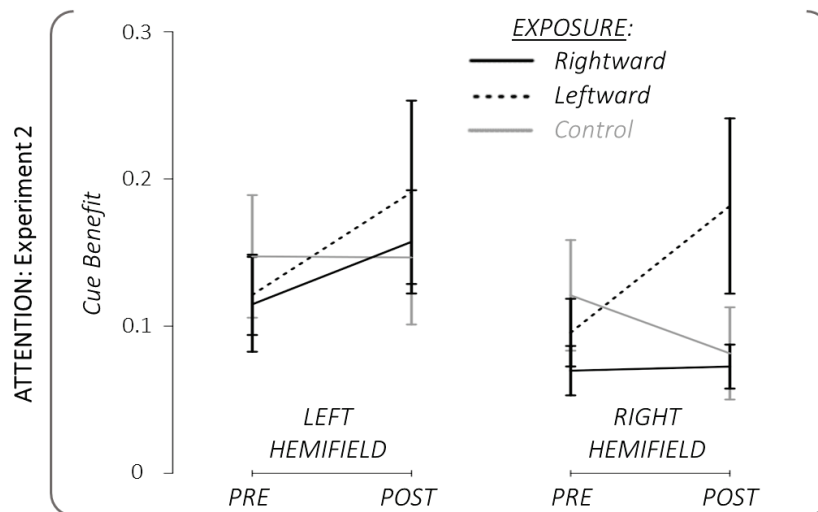


Figure 7: Pre- and Post-exposure attention results in Experiment 2. Group mean (+/- SD) of cue benefit for the pre- and the post-exposure phases in the two hemifields of target presentation. Black lines: rightward adaptation exposure; Black dotted: leftward adaptation exposure; Grey lines: control exposure.

As for Experiment 1, the performance in the attention task of Experiment 2 was evaluated by computing the subjects' cue benefit (Figure 7). The 3-factor rmANOVA (exposure x phase x target hemifield) revealed no significant main effect (Phase: partial $\eta^2 = 0.10$; $F_{(1,17)} = 1.98$; $P = 0.18$; Target hemifield: partial $\eta^2 = 0.11$; $F_{(1,17)} = 2.00$; $P = 0.18$; Exposure: partial $\eta^2 = 0.49$; $F_{(2,34)} = 0.07$; $P = 0.29$). The following interactions were not significant: double interactions (Exposure x target hemifield: partial $\eta^2 = 0.09$; $F_{(2,34)} = 1.59$; $P = 0.22$; Phase x target hemifield: partial $\eta^2 = 0.05$; $F_{(2,34)} = 0.95$; $P = 0.34$), and the triple interaction (Exposure x phase x target hemifield: partial $\eta^2 = 0.05$; $F_{(2,34)} = 0.92$; $P = 0.41$). However, the double interaction exposure x phase was significant (partial $\eta^2 = 0.18$; $F_{(2,34)} = 3.76$; $P = 0.03$; achieved power > 99%).

Post-hoc paired Student t-tests revealed that, irrespective of hemifield, the differences between the pre- and the post-exposure phases for the control exposure and for the rightward adaptation exposure did not reach significance ($t_{(35)} = 0.92$; $P=0.36$; $t_{(35)} = -1.53$; $P=0.13$; respectively). In contrast, the exposure to leftward adaptation induced a significant difference between the pre- and the post-exposure, yielding an increased cue benefit in both hemifields (from 0.11 to 0.19; 95 CI mean difference = [-0.14; -0.02]) after SA ($t_{(35)} = -2.56$; $P=0.015$ (FDR- corrected $P = 0.045$); Cohen's $d = 0.40$).

Concerning the link between the change in the left saccadic gain and the change in the cue benefit (Figure in Supplementary), after leftward adaptation, we did not highlight a significant correlation ($r_{(35)} = 1.30$; $P = 0.21$).

In summary, the adaptation of leftward saccades resulted in significantly increased attention performance when the target was presented at 3° in both the adapted and unadapted hemifield, but without relationship with individual variations of the level of adaptation.

4. Discussion

The present study questioned the link between the oculomotor and visuospatial attention systems, by testing the effect of sensorimotor plasticity of VS on covert endogenous orienting of attention. Based on a within-subjects comparison between leftward adaptation, rightward adaptation, and control exposure, we found the cueing effect on discrimination RT to increase specifically after leftward adaptation for discrimination stimuli at 3° in either (adapted or unadapted) hemifields. These results demonstrate for the first time a boosting effect of oculomotor plasticity on endogenous orienting of attention in healthy humans, deepening our knowledge of saccadic adaptation mechanisms and providing evidence for shared neuronal representations for eye movements and visuospatial attention.

As mentioned in Introduction, a coupling between SA and covert shifts of attention has been reported only once at the behavioral level in a previous study from our lab (Habchi et al., 2015). However, contrary to the Posner-like paradigm used here, the detection task Habchi and colleagues used could not entirely distinguish attention orienting from other potential cognitive or motor components. In addition, they investigated exogenous attention orienting. Here we decided instead to focus on the voluntary/endogenous modality, because it has been suggested to refute the premotor theory of attention (Smith and Schenk, 2012). The present demonstration of a coupling in this latter modality therefore provides a new piece of empirical argument in this debate.

Interestingly, despite these differences, in both Habchi and colleagues' study and ours, the coupling was observed only after adaptation of leftward saccades. They interpreted this saccade direction specificity as resulting from the known dominance of the right hemisphere in controlling exogenous attention as compared to the endogenous orienting of attention believed to be more symmetrical (Corbetta et al., 2008). A similar interpretation of the saccade-direction specific coupling demonstrated here for the voluntary/endogenous modality is not straightforward in this framework. However, TMS studies have suggested that, although both left and right IPS play a role in voluntary orienting visuospatial attention, the right hemisphere has a dominant contribution. Capotosto and colleagues (Capotosto et al., 2012; Capotosto et al., 2009) reported that the disruption of the right IPS, and not the left IPS nor the right FEF, led to a bilateral alpha band synchronization in the occipito-parietal cortex and therefore to a

decreased efficiency of target processing in both hemifields. The impact of the right IPS disruption was also observed in two studies (Ruff et al., 2008; Ruff et al., 2009) using concurrent TMS/fMRI in which stimulation of right but not left posterior parietal cortex caused changes of fMRI activity bilaterally in the occipital lobe. Within this framework, the presently demonstrated effect of adaptation of leftward, but not rightward, VS could be interpreted as a further evidence for right hemispheric dominance in visuospatial attention. In addition, the benefit in the two hemifields that we found in the attention task is consistent with the above mentioned TMS studies. Indeed, it can be postulated that SA of leftward saccades, contrary to the disrupting effect of TMS, increases brain excitability in the rIPS and therefore modulates neural excitability in the occipital cortex bilaterally.

Other previous investigations of the link between SA and visuospatial attention have all focused on the so-called pre-saccadic shift of attention, corresponding to an enhanced perception which automatically occurs at the saccade target location just before saccade initiation (Deubel and Schneider, 1996). These studies have shown that after saccadic adaptation, the spatial locus of highest perceptual performance remains coupled with the saccade endpoint, not to the visual target (Doré-Mazars and Collins, 2005; Collins and Doré-Mazars, 2006; Collins, 2010a; but see Ditterich et al., 2000). In line with the premotor theory of attention (Rizzolatti et al., 1987), this observation reflects an adaptation-related change of a prediction of saccadic commands, which is also consistent with the proposal that oculomotor efference copy is modified after adaptation (Collins, 2010a).

The present findings clearly point to a new oculomotor plasticity-visuospatial attention coupling as compared to the studies mentioned above. First, the lack of significant correlation between the adaptation rate and the cue benefit boost does not illustrate the metrical relationship found in previous studies between saccade size and endpoint of pre-saccadic attention shift (Schneider and Deubel, 1995). Together with the specificity to a 3° eccentricity, this observation suggests an all-or-none effect restrained to the peri-foveal part of the visual field. Second, we demonstrated an effect of SA on covert shifts of attention, unrelated to any oculomotor preparation, as subjects always kept central fixation throughout the attention tasks. Thus, possible changes of oculomotor efference copy are unlikely to play any role in our experiments. Furthermore, the discrimination performance did not change for a target at 7.5°, *i.e.* the eccentricity which matched best the adapted saccade endpoint. Thus, the coupling we report is not related to the new metric of the adapted saccade, and not to the adaptation field (Frens and Van Opstal, 1994; Noto et al., 1999). Instead the boosting effect was actually found at the eccentricity of 3° which corresponds to the size of the target jump eliciting SA. This raises the interesting possibility that it is the systematic exposure to the error signal driving SA, rather than the oculomotor changes related to SA itself, which drives the changes in covert attention. Recall however, that the same target jump and error signal were induced during the control exposure, but 805 ms after the saccade, a delay which prevented SA to be elicited. We thus believe that, to be able to boost visuospatial attention, the systematic error signal induced by target steps must engage plasticity mechanisms. Further experiments would allow to better understand the mechanisms underlying the coupling demonstrated here. One could test the effect of adaptation of larger saccades with larger target jumps and test whether the eccentricity where the boosting effect occurs changes accordingly or remains peri-foveal part of the visual field.

Another possible explanation of this limitation to the peri-foveal part of the visual field is a SA-induced compression of represented visual space (in case of backward adaptation) that would shift the representation of visual stimuli toward the center of gaze. Indeed, Zimmermann and Lappe (2009; 2010)

showed that SA induces a shift of the subjectively-perceived location of objects flashed before a saccade or during fixation, suggesting that spatial visual representations are shaped by oculomotor planning (Collins et al., 2007; Zimmermann and Lappe, 2016). Consequently, when subjects have to localize (Zimmermann and Lappe's) or discriminate (current study) such perifoveal stimuli, they would both underestimate the targets eccentricity and discriminate them with a faster reaction time. The functional coupling between adaptation and attention, highlighted by the present results, strongly suggests that the corresponding neural substrates overlapping at the macroscopic level (see Introduction; Gerardin et al., 2012; Panouillères et al., 2014; Corbetta and Shulman, 2002) actually host neuronal population co-activated for saccades and attention. Although neuronal recordings in the monkey posterior parietal cortex have provided evidence for distinct neuronal populations for orienting of attention and saccadic eye movements (Liu et al., 2010), other studies have suggested that the monkey LIP hosts priority maps used both by attention and eye movements to select targets (Bisley and Goldberg, 2010). Therefore, we believe that SA acts on such 'common priority maps', thereby transferring to covert attention mechanisms. Common priority maps for attention and eye movements may have been implemented in the course of natural selection because sharing neural substrates for cognitive functions is advantageous in terms of neural resource.

The hypothesis of shared neural resource between adaptation and attention predicts the existence of another functional coupling, opposite to that reported here, *i.e.* from attention to saccadic adaptation. Indeed, some studies have suggested that attention shifts affect SA. Flashing in the vicinity of a stationary saccade target a stimulus attracting exogenous attention, a perceptual target (Schutz et al., 2014) or a salient visual distractor (Khan et al., 2014), is sufficient to induce SA. Further, McFadden et al. (2002) showed that it is possible to adapt the exogenous shift of attention by 'stepping the attentional target' during a covert attentional task, and that such 'adapted attention' transferred to saccades. Finally, SA efficiency has been shown to increase with attentional load (Gerardin et al., 2015). The hypothesis of shared neural substrates between adaptation and attention also predicts that some neural changes related to SA can be detected in the attentional task performed immediately after, akin to the change of gamma band activity we could disclose recently, albeit in the exogenous/reactive modality (Nicolas et al., 2018). A similar magnetoencephalographic study will be required to disclose whether the coupling between adaptation of voluntary saccades and endogenous attention is subtended by an increased brain activity, reflected in the gamma band, in the region of the IPS of the dorsal attention system.

Taken together, this study highlights a functional coupling between adaptation of voluntary saccades and endogenous visuospatial attention. This finding provides deeper insight into the role of the motor system in the updating of visual space representations, and leads toward promising rehabilitation procedure for patients with visuospatial disorders.

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Experimental contributions

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Study 3: Effect of VS adaptation on endogenous orienting of attention

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3.2. Supplement

Supplementary methods

Power analysis. The number of subjects was determined from the following power analysis performed through the G*Power software (Faul et al., 2007). As stated in Introduction, we are aware of only one previous study testing the coupling between SA and visuospatial attention (Habchi et al., 2015). This study disclosed that after adaptation of RS in the left hemifield, the performance in a visual detection task improved in the left hemifield. This was revealed by a significant 3-level interaction in a repeated measures ANOVA (rmANOVA) with subjects as the repeated measure, the target hemifield (left or right), the phase (pre- or post-exposure) and the exposure (leftward adaptation, rightward adaptation, or control) as within-factors. We have computed the effect size of this interaction and found a value of 0.41 (Sum of Square of the numerator = 485.7; Sum of Square of the denominator = 695.8), resulting in an achieved power larger than 99% according to the G*Power software. However, since the present study will address another modality (*i.e.* voluntary saccades and endogenous attention), we decided to reduce this effect size to a conservative level of 0.2.

Given this medium effect size ($f = 0.2$), we found that 14 subjects are required for our interaction of interest between the 3 within-subjects to reach a power of 95.3% when assuming an average correlation coefficient of $r = 0.85$ between repeated measures and a nonsphericity correction of $\epsilon=0.5$ (see below). To counterbalance the six possible testing orders in the sessions included in our design, we decided to increase for each experiment this number up to 18 subjects, reaching a power of 98.9%.

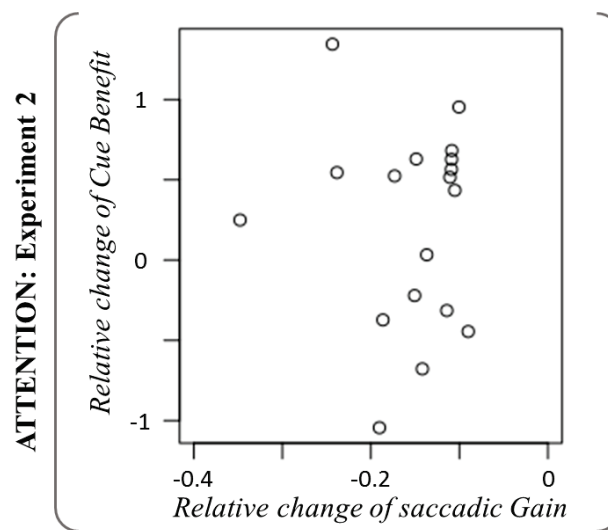
The power analysis is also based on a pilot study we performed to find the best Stimulus Onset Asynchrony for our endogenous task. The SOA, the duration between the cue appearance and the target appearance, is the time allocated to endogenous attention to shift and develop. Our pilot study consisted in testing the attention task described in the main text (see Attention task: visual discrimination in the section Apparatus, stimuli and procedure of the MATERIALS AND METHODS) for 3 different SOAs (602 ms / 850 ms and 1106 ms), each SOA condition being evaluated in a separate session comprising 3 blocks of 52 trials. These pilot data (RT of discrimination response) allowed us to establish a main effect of cue type regardless of the SOA duration (effect size = 0.88; $F(1,3) = 22.3384$; p -value = 0.0179). No main effect of SOA nor interaction between SOA and cue type was significant. They also allowed us, using the Mauchly's test for sphericity, to check that the sphericity of the 3-level factor SOA is respected ($W=0.27$; p -value = 0.279). Finally, these data allowed us to determine the correlation between repeated measures: the correlation of discrimination RT between the three SOA conditions (602 ms *versus* 850 ms, 602 ms *versus* 1106 ms, and 850 *versus* 1106 ms), using Pearson's product moment correlation coefficient tests, turned out to be highly significant in all three cases (p -values < 10^{-5} and r -values > 0.85). We therefore set the correlation between repeated measures at $r=0.85$.

Staircase procedure. Before the pre-exposure phase of the first session, a staircase procedure allowed us to determine the gabor patches contrast, separately for each subject and each hemifield. A transformed 3-down 1-up procedure was used (Levitt, 1971; Leek, 2001). For each hemifield, one staircase starting with a median contrast (50%) was run, leading to 2 interleaved staircases. A staircase trial consisted of the same sequence of events as in the attention task except that all cues were uninformative and the time between the cue and the target reduced to 500 ms. The procedure ended as soon as it reached 15 reversals in each hemifield. The final contrast was determined separately for

each hemifield by averaging the 4 last reversal values. Before the staircase procedure, subjects performed at least 25 trials of practice with a gabor patch of 100% contrast (20 trials plus five consecutive correct trials). The following instructions were displayed at the beginning of the practice block: “clockwise or anti-clockwise?; clockwise => push; anti-clockwise => pull”. The experimenter displayed an example of both types of trial (informative and uninformative) and could repeat the examples until the subject got familiar with them.

Instructions and feedback. After the staircase procedure was completed, and when the subject was ready, the attention task started by first displaying on the screen instructions on the use of the cue. These instructions were read as follows (translation from French): “Now, you will have arrows to help you; RIGHT arrows => RIGHT target; LEFT arrows => LEFT target; OUTWARD arrows => RIGHT or LEFT; INWARD arrows => DO NOT ANSWER”. Then, we displayed instructions on how feedback about their discrimination performance are provided after each block of trials, namely by means of a gauge filling up or down depending on subject’s performance (“if you use the arrow well enough to be fast and accurate, the gauge will fill up otherwise it will empty”). At the beginning of each session, this 10 graduations gauge was initially filled to the fourth graduation. At the end of each block the gauge was presented again but filled to a new graduation according to the subjects’ score during the block: one graduation was gained if they were either faster or more accurate in informative trials than in uninformative trials, two graduations was gained when the two criteria were met, and conversely, one graduation was lost if either subjects’ median performance was slower and less accurate in informative trials than in uninformative trials or if their overall performance is less than 70% correct. Increases or decreases of gauge levels were emphasized by a green or red filling color, respectively. In addition, changes of gauge level were accompanied by the following sentences: “Be careful, you need to better use the arrows” (one graduation down), “Good, but you can still better use the arrows” (one graduation up); “Bravo, keep on using the arrows this way!” (two graduations up). This procedure aimed to reinforce the use of the cue without favoring either speed or accuracy. Finally, a sentence was displayed requesting the subject to signal when she/he was ready to start the next block. These written feedbacks and instructions are intended to avoid non-standardized oral feedback from the experimenter who was not blind regarding the type of session (leftward adaptation, rightward adaptation, control).

Supplementary results



Supplementary Figure 1: Relative change of cue benefit (irrespective of hemifield) in function of relative change of saccadic gain in the leftward adaptation exposure. Points represent individual data.

Supplementary references

Faul F, Erdfelder E, Lang A-G, Buchner A (2007) G* Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behavior research methods* 39:175–191.

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General discussion



1. Summary of the results

This section provides the main results of our three studies (Figure 43). We also briefly discuss some points that will not be further discussed in the following section (On trying to make sense, 2).

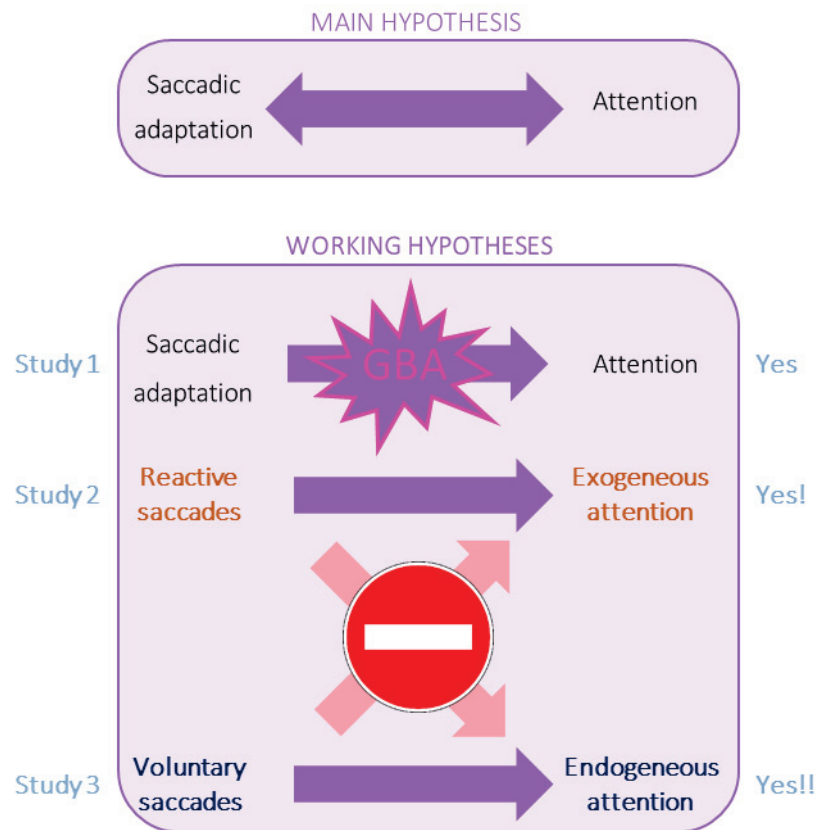


Figure 43: What happened between page 88 and page 165. Upper panel: The main hypothesis predicts a bidirectional functional coupling between saccadic adaptation and attention. Lower panel: SA increased Gamma Band Activity (GBA) in a large network including the ventral network of exogenous attention. RS adaptation boosted exogenous orienting of attention and VS adaptation boosted endogenous orienting of attention.

1.1. Study 1: Gamma and SA

Through continuous recordings of the brain magnetic fields and eye position, this study aimed to investigate the neural underpinnings of the coupling between SA and attention. We studied the effect of backward adaptation of leftward RS on the pre-target power in the gamma frequency band, referred to as gamma band activity. The pre-target GBA was analyzed during the exposure to SA and during the subsequent saccadic and detection tasks. The rationale was that those mechanisms which are activated during the SA procedure and which underlie the SA-attention coupling, should leave a trace in the CNS which could still be detected during the subsequent saccadic and detection tasks. We predicted that this trace should be measured as a change of pre-target GBA reflecting baseline neuronal excitability, regardless of the target processing or of the computation of post-saccadic error.

General discussion

This study was a replication of the second experiment reported in Habchi et al. (2015) adapted to the MEG constraints (increased number of trials and change of display further detailed below). The experiment comprised two sessions which differed only by the exposure: in one session the exposure induced backward adaptation of leftward saccades (SA exposure), in the other session the subjects executed un-adapted leftward saccades (control exposure). The order of these sessions was counterbalanced among the 12 healthy human subjects. Before the exposure session (either control or SA), subjects performed a covert speeded discrimination task. They were presented with targets that were unpredictable in time and position and were instructed to answer with their dominant hand whether the target appeared in the right or left hemifield. They then performed a saccadic task to evaluate saccade amplitude before the exposure. After the exposure, subjects performed the same saccadic task to evaluate the changes on saccadic amplitude and finally performed the same speeded discrimination task to evaluate the effect of SA on RT.

The main finding is that saccadic adaptation increases the GBA activity in a widespread brain network. During the saccadic task immediately after the exposure, this increase was found in the right hemisphere centered on the TPJ and including area MT/V5. As the analysis contrasted between SA and control exposures, this increase could be specifically linked to saccadic adaptation. This result echoes the Gerardin et al.'s (2012) findings, namely that the adaptation of leftward RS recruited the TPJ, area MT/V5 (and also the inferior precentral sulcus not highlighted in our study) in the right hemisphere. During the subsequent discrimination task, the GBA increase was more prominent in the left hemisphere and the medial part of the right hemisphere. The fact that we only found a small overlap between the networks highlighted in the saccadic and the discrimination task can be explained by the difference in the tasks. Indeed, during the discrimination task, no eye movements were allowed, whereas in the saccadic task, well, of course, subjects made saccades.

In addition, a correlation analysis (Supplement, 1.2 in the Experimental contributions) revealed that the individual relative change of GBA correlated with the individual relative change of saccadic amplitude during the first block of the exposure to SA. This correlation finding further supports that the GBA increase is due to SA. Brain areas where such correlation was found are restricted to the right parietal cortex, which has consistently been involved in both saccade generation and orienting of attention (see State of the art).

Finally, one unexpected result was the unspecific decrease of RT during the discrimination task. Indeed, the acceleration of detection performance in the post-exposure phase was observed regardless of the exposure condition or of the hemifield of target presentation, contrary to our expectations derived from Habchi et al.'s (2015)'s results. Our interpretation of this discrepancy is that in the setup changes due to the MEG constraints, the visual target displayed a 100% contrast while in Habchi et al.'s (2015) experiment, the target contrast was 50%. In the Visuospatial attention section (section 3 of State of the art) we mentioned that attention acts on visual contrast sensitivity. In our experiment, the contrast was ceiled, therefore, it might be that the behavioral expression of the SA-induced boosting effect was masked. Concerning the GBA increase in the left hemisphere during the subsequent discrimination task, it can be postulated that this activation reflects the restoration of the baseline activity, *i.e.* before adaptation. The easiness of the task might have prevented the activation of the ventral network of attention. This under-activation might have launched processes of re-balancing between the left and the right PPC involving an increase of GBA in the left hemisphere.

To conclude, this study provided a potential neural mechanism of the oculomotor plasticity - attention coupling (Nicolas et al., 2018). The unexpected behavioral results of this experiment constituted one of the motivations of our study 2.

1.2. Study 2: Effect of RS adaptation on exogenous attention

The motivations for this study were: (1) to solve the discrepancy between the behavioral results of our study 1 and Habchi et al.'s (2015) by decreasing the contrast of our targets and (2) to circumvent the limits of the speeded discrimination paradigm employed in these two studies. Indeed, as presented in the State of the art, attention relates to three systems: the alerting system, the executive system, and the orienting system. In the speeded discrimination paradigm, the orienting system was not manipulated. Therefore, it was not possible to disentangle whether the accelerated RT were due to a boost of alertness, of the orientation of attention, of motor preparation, or in decision making. Study 2 therefore aimed at investigating the coupling between SA and the orienting system of attention in the reactive/exogenous modality. Our prediction was that the adaptation of leftward RS will boost the exogenous orienting of attention system. Furthermore, this boost should be spatially selective and concern only the orienting of attention towards the left hemifield. Moreover, to extend our knowledge on the coupling between SA and attention, we investigated both backward and forward adaptation of leftward saccades. We did not investigate the rightward saccades since Habchi et al. (2015) did not report an effect of SA in the right hemifield.

The structure of this experiment resembles that of study 1, particularly the pre-/post-exposure design used to measure the effect of SA exposure on saccadic amplitude and attentional performances. However, these two studies differed in the following aspects. First, we decided to investigate forward adaptation in Study 2. Therefore, each of the 18 healthy human subjects underwent three exposure types in a counterbalanced order: backward adaptation, forward adaptation and control. Second, a covert attention Posner-like paradigm was designed to measure the performances specifically related to the exogenous orienting of attention. This implied that the targets were preceded by a peripheral cue, with a short SOA (98 to 292 ms). Moreover, our prediction concerned the benefit of attention, therefore we only presented informative cues (100% valid, no invalid) and uninformative cues. The relative change of RT between the informative trials and uninformative trials was our measure of the orienting of exogenous attention and is referred to as the cue benefit.

The major finding of study 2 is that the backward adaptation of leftward saccades increases the cue benefit in the left hemifield. This boost is observed for the four target eccentricities. Moreover, the adaptation rate and the cue benefit boost are not significantly correlated, suggesting an all-or-none boosting effect. However this boost started in the second block and reached significance in the third block of the attentional task. This latter finding suggests that the boosting effect developed on a slow time-course. The finding of the hemifield selectivity was in our prediction. Indeed, we discussed in the State of the art, the dominance of the right cerebral hemisphere for attentional processes (left hemifield), especially concerning the exogenous orienting system.

Another finding is that the forward adaptation of leftward RS did not boost the orienting of attention assessed by the cue benefit. Forward and backward adaptations are two distinct processes underpinned by different neural substrates already at the level of the cerebellum (see section 2 in the State of the

art, Oculomotor plasticity). One possible explanation is that the cortical substrates underlying forward adaptation are partially distinct from those of backward adaptation and do not overlap with the neural substrates of the attentional system.

Finally, we found that the cue benefit decreased after the control exposure but this was not hemifield specific. Our interpretation is that the orienting of attention was a victim of subjects' fatigue. Moreover, this result can help to understand the slow time course of the boosting effect that we found after backward exposure of leftward saccades. Indeed, it is possible that the boosting effect had first to counteract the fatigue effect to finally boost the cue benefit. The task in Habchi et al. (2015) did not manipulate the orienting of attention and might have been less tiring for subjects, explaining why an immediate rise of the boosting effect seemed to occur in this study. Yet, as this was not explicitly tested, a slow build-up of the boosting effect cannot be excluded in their study.

To conclude, study 2 confirmed that the backward adaptation of leftward reactive saccades benefits to the exogenous orienting of attention. This boosting effect is hemifield specific since it was observed only in the adapted (left) hemifield. Moreover, study 2 disclosed that no such boosting effect could be elicited by forward adaptation.

1.3. Study 3: Effect of VS adaptation on endogenous orienting of attention

In our hypotheses, we proposed that the segregation of the cortical substrates between SA of VS and RS overlaps with the segregation of the attentional networks between exogenous and endogenous orienting of attention. We studied the effect of RS adaptation on exogenous attention in study 1 and study 2. In the present study 3, we were interested in the effect of adaptation of VS on endogenous orienting of attention. While Habchi et al. (2015) tested, through their speeded detection task, the inter-modality link between VS adaptation and exogenous attention, and found none, the modality specific coupling between VS adaptation and endogenous attention has never been tested so far. Therefore, we limited our investigation to the backward adaptation. However, since the endogenous orienting system is known to be symmetrical, we were interested in the effect of adaptation of either leftward or rightward saccades, tested in two separate sessions compared to a control exposure session (within-subjects design). Our prediction was that covert endogenous orienting will be boosted by the backward adaptation of both leftward and rightward VS: the benefit of attention in the left hemifield should increase after exposure to SA in the left hemifield, and the performance in the right hemifield should increase after exposure to SA in the right hemifield. This prediction is extrapolated from Habchi et al.'s (2015) results. However, this previous study involved the attentional exogenous orienting network which is lateralized to the right hemisphere, whereas the endogenous network of attention recruited in this discrimination task is more bilateral. Therefore, extrapolation from these previous studies to the present one might not completely hold, and an increase of attentional performance in both hemifields after SA could also be predicted.

This study differs also from the previous studies 1 and 2 because it comprises two identical experiments, testing separately two different target eccentricities. In the first experiment, the targets were displayed at an eccentricity of 7.5° whereas in the second the target eccentricity was 3°. This block design was aimed to reinforce the endogenous orienting of attention. The assessment of covert attentional endogenous orienting was done using a Posner-like paradigm with central cues which were either

informative (100% valid) or uninformative. In this study, we again used the relative change of RT between informative trials and uninformative trials, referred to as the cue benefit, as a measure of the orienting of attention.

The main result of this study is that the backward adaptation of leftward, but not rightward, VS boosted the cue benefit for targets presented at an eccentricity of 3° but not of 7.5°. Moreover, the adaptation rate and the cue benefit boost were not significantly correlated, suggesting again an all-or-none boosting effect. This effect was however not specific to the adapted hemifield, being revealed both by -3° and +3° targets. Neuroimaging studies have shown that the endogenous orienting of attention activated the dorsal network in both hemispheres (although this activation was stronger for the contralateral one) probably accounting for this effect.

Interestingly, we found again that only leftward adaptation produces a boosting effect on orienting of attention. In the absence of neuroimaging investigation of the adaptation of rightward saccades, we hypothesized that the regions activated by rightward VS adaptation would be the same as those of leftward adaptation but in the left hemisphere counterparts. Our results do not confirm this prediction and rather open the possibility that SA and/or attention substrates are not symmetrical and, in any case, do not overlap with the attentional network of the left hemisphere.

To conclude, study 3 highlighted that the backward adaptation of leftward voluntary saccades benefits to the endogenous orienting of attention. Moreover, this boosting effect is spatially restricted around the fovea since it was observed in the two hemifields for targets at 3° but not 7.5° of eccentricity.

2. On trying to make sense

This section will discuss the results summarized above. We will first discuss the different and common points between the adaptation types, namely between leftward vs rightward saccades, between RS vs VS, and between forward vs backward ISS. We will then discuss the mechanisms underlying the boosting effect in the different adaptation types. Finally, we will propose a theoretical framework underlying the systemic and neural processes at work during saccadic adaptation and explaining the subsequent effect on orienting of attention.

2.1. Difference between adaptation types

2.1.1. Direction of the adapted saccade (rightward vs leftward)

We tested both rightward and leftward VS adaptation effects in study 3. In study 2, we did not test the rightward adaptation, however Habchi et al. (2015) had already disclosed that only adaptation of leftward RS, but not of rightward RS, did boost the detection performances. Therefore, although we should experimentally confirm that, we will assume that the orienting of attention is only affected by adaptation of leftward saccades.

In the State of the art, we mentioned that the ventral network of attention (localized in the right hemisphere) is activated for the orienting toward the entire visual field while the dorsal network of attention was more spatially specific in the sense that a given hemisphere is preferentially activated by contralateral cues as compared to ipsilateral cues. Initial predictions could have been that the leftward RS adaptation will affect the orienting of attention towards the two hemifields while both leftward and rightward VS adaptation would benefit to attention orienting in the contralateral field (right and left, respectively). However, our results do not support these predictions but data in the literature can help to understand the present results.

Concerning RS adaptation, one can postulate that the hemifield specificity of the observed boosting effect emerges from the known dominance of the right hemisphere in the exogenous orienting of attention. Indeed, normal subjects display an attention bias towards the left hemifield as evidenced by the 'pseudo-neglect' effect in the line bisection task. Moreover, the prism adaptation exposure is known to induce rightward biases in visuospatial tasks when leftward-deviating prisms are used in healthy subjects (Bultitude and Rafal, 2010; Bultitude et al., 2013; Colent et al., 2000; Loftus et al., 2009) whereas rightward-deviating prisms do not induce leftward biases (Schintu et al., 2014; Bultitude et al., 2013). Bultitude and colleagues' study further showed that the leftward PA actually influenced spatial remapping in the left visual field and not in the right visual field. Taken together, these observations lead us to suggest that leftward RS adaptation creates an imbalance between the right and left parietal cortices and further enhances the leftward bias resulting in a faster orienting toward the left hemifield.

Concerning VS adaptation, we found that leftward backward adaptation, and not rightward backward adaptation, boosted orienting towards targets at an eccentricity of 3° in both hemifields. The fact that only leftward adaptation resulted in such effect can suggest, similarly to the arguments developed for RS adaptation, that the dorsal network of attention is not as symmetrical as usually claimed. Indeed, studies using TMS only or TMS combined with fMRI have provided evidence that the right posterior IPS,

and not the left posterior IPS (nor the right FEF), modulates brain activity in bilateral occipital visual areas (Capotosto et al., 2009; Capotosto et al., 2012; Ruff et al., 2008; Ruff et al., 2009). The disruption of the right IPS led to an increased synchronization in the alpha band or in BOLD activity in the left and right occipital lobes. From these studies, one can infer that leftward SA would have an opposite effect to TMS, resulting in larger desynchronization of alpha activity in the occipital areas, bilaterally, and hence in enhanced orienting of attention in both hemifields.

To conclude, adaptation of both leftward VS and RS is effective in boosting orienting of attention while rightward saccadic adaptation is not. From this we posit that the neural recipients for the functional coupling between attention and adaptation does not have a counterpart in the left hemisphere, a suggestion holding for both VS and RS.

2.1.2. Type of the adapted saccade (VS vs RS)

In the section just above, we discussed that both leftward RS and leftward VS backward adaptation are effective in boosting orienting of attention. However, the results highlighted by these two types of adapted saccades are different in some aspects. The main difference in the results found after RS and VS adaptation, is that RS adaptation elicited a boost in the entire left hemifield (hemifield specific) whereas VS adaptation boosting effect was restricted to targets presented close to the fovea (3° and not 7.5°) regardless of the hemifield (spatially restricted). This difference between RS and VS adaptation concerning the spatial pattern of the boosting effect might reflect a difference of adaptation sites in the brain for each modality.

Concerning VS adaptation effect, a possible explanation is a backward SA-induced compression of space limited to the peri-foveal part of the visual field. This compression would shift the representation of visual stimuli towards the center of gaze. Indeed, Zimmermann and Lappe (2011b) showed that mislocalization after VS adaptation was more prominent than after RS adaptation. Furthermore, their results showed that VS adaptation was more affected by the eye position than RS adaptation, suggesting that VS uses a non retinocentric reference frame. The use of this type of reference frame requires the visual space representation to be updated after SA.

The mechanisms of backward RS adaptation may be different. Indeed, backward RS adaptation is believed to rely on an alteration of the saccade trajectory rather than on a change of visual target mapping (Ethier et al., 2008a). Moreover, the boosting effect we found after RS adaptation was found for the entire range of tested eccentricities in the left hemifield (from 3° to 15°). Note however that this broad effect can relate to the broadness of the adaptation field (see State of the art). Although we did not test the adaptation field in this experiment, the literature suggests that it is broad enough to include the different target eccentricities tested in our experiment. Thus, the coupling between RS adaptation and attention might arise as a result of SA-related changes at a motor level.

The hypothesis of different adaptation sites is further supported by the asymmetrical transfer of adaptation. Indeed, the transfer of adaptation of VS to RS is larger than the reciprocal transfer (Alahyane et al., 2007; Cotti et al., 2007; Collins & Doré-Mazars, 2006; Zimmermann & Lappe, 2009), possibly due to an upstream neural site for VS adaptation as compared to RS adaptation. This difference of adaptation sites could account for the transfer of SA boosting effect to both hemifields in the

voluntary/endogenous modality and not in the reactive/exogenous modality. Indeed, Cotti et al. (2007) showed that adaptation of VS, but not of RS, transfers to hand pointing movements. Also, Zimmermann and Lappe (2009) reported that RS adaptation led to a mislocalization of flashed probes whereas VS adaptation led to a mislocalization of both flashed and stationary probes. These results suggest that RS and VS adaptation act on spatial cognition at different levels. (Collins et al., 2007a; Zimmermann and Lappe, 2016) suggested that oculomotor planning shape the visual representation but this might be restricted to VS adaptation since, as suggested by Ethier et al. (2008a), VS adaptation relies on change of target representation, either at the level of the SC or upstream, while RS adaptation would rely on change at the motor, subcortical, level.

Since VS and RS adaptation rely on different mechanisms and likely act at different levels of sensorimotor transformation, their effect on orienting of attention could also be different. VS adaptation boosting effect could rely on compression of space while RS adaptation effect could rely on an increased bias of the exogenous orienting system for the left hemifield. Moreover, effects of VS adaptation observed at the level of the PPC could be sent downstream, to sensory areas; while RS adaptation effect could be restricted to the areas in the ventral network of attention and would only act on the readiness of the breaking circuit it represents.

To conclude, both VS and RS adaptation led to a boosting effect on orienting of attention. The mechanisms underlying them may be different since in the case of RS, the effect was hemifield specific while in the case of VS the effect was restricted around the fovea but for both directions of orienting shifts.

2.1.3. Direction of the error signal (backward vs forward)

In this set of experimental work as well as in the literature, the effect of forward adaptation on covert orienting of attention has only been tested in the reactive modality. The study reported by Wick et al. (2016) addressed the effect of either forward or backward RS adaptation on attentional performances, but on the static attentional field as measured in a visual detection task with flankers, and with adaptation of vertical saccades. Yet, just like in the present work, their results showed that only backward, and not forward adaptation, had an effect on the attentional field, reducing its extent.

As already mentioned in the previous section, backward RS adaptation is believed to correspond to an alteration of the saccade trajectory, contrary to forward RS adaptation that would result from a target remapping process (Ethier et al., 2008a). This distinction echoes the one raised above between VS and RS. In this framework, it might be possible that the effect of forward RS adaptation would rely on a visual remapping process. However, since forward adaptation takes longer to develop and to consolidate, the number of trials used in this experiment might have been insufficient to produce a significant boosting effect. This suggestion is supported by the fact that after control exposure, the cue benefit decreased while it remained equivalent between the pre- and the post-exposure phases in the forward adaptation condition. Given the fatigue effect on cue benefit postulated above, the stability of the cue benefit in the forward adaptation condition might in fact reflect a small boosting effect just able to maintain orienting of attention against fatigue. In this case, a novel experiment with an increased number of forward adaptation trials should be able to disclose a boosting effect different from the one observed after backward RS adaptation. Indeed, if forward adaptation of RS induces a remapping of visual space

like backward adaptation of VS, the pattern of the results would resemble that obtained after backward VS adaptation, namely a performance boost occurring at a peri-foveal location in both hemifields.

Finally, when considering the difference between forward and backward adaptation, the mere effect of the direction of the ISS has to be discussed. Indeed, backward ISS simulates the visual consequence of a hypermetric saccade while forward ISS results in a hypometric post-saccadic visual error. The saccadic system is hypometric by default, therefore, the backward adaptation related hypermetria breaks this default state and automatically launches adaptive corrections of the motor command. In the forward adaptation on the contrary, the saccadic system remains in this default *normal* situation, with a hypometric error which is simply enhanced by the ISS. In this latter case, the system has first to *decide* whether this error is an error at all and whether it is worth it to correct, involving more cognitively-driven processes than in the case of backward adaptation. This explanation would first explain why the time course of forward adaptation is slower than that of backward adaptation. Second, if forward adaptation relies more on cognitively-driven processes, it might be possible that it does not act on exogenous orienting of attention but would instead act on the endogenous orienting of attention. This latter proposal is consistent with the fact that studies on the effect of SA on visual localization consistently showed stronger mislocalization after forward adaptation as compared to backward adaptation.

To conclude, the backward, but not the forward, adaptation led to a boosting effect on orienting of attention. The reason(s) are yet unclear but we will try to encompass these results in the proposed mechanisms detailed below (Conclusion on saccadic adaptation effect, 2.2.2.2).

2.2. On what relies the link between SA and attention

In the previous section, we discussed the differences between adaptation types. We suggested that these differences could be related to different mechanisms supporting the boosting effect highlighted in RS and VS adaptation. In the case of VS, this hypothesis would imply that there is a common site between space representation and saccadic adaptation where the interactions allow the latter to shape the former. In the case of RS, the increased excitability of the ventral system of orienting of attention could be responsible for and enhance the leftward bias. Note however, that VS adaptation could also be explained in the framework of an increased brain excitability in the dorsal fronto-parietal network.

In the following, we will first argue for the hypothesis of a boosting effect due to remapping of the visual space restricted to VS adaptation. We will then propose and favor that VS and RS adaptation boosting effects are actually subtended by the same mechanism, namely an increased brain excitability in the fronto-parietal network.

2.2.1. Updating of visual space representations

2.2.1.1. Forward model

The forward model is the mechanism that computes the predictions of the sensory consequences of a movement based on the upcoming motor command. The cerebellum has been proposed to be the neural recipient of this mechanism in SA (Ethier et al., 2008a) as well as for motor learning in general (Ito, 2013; Wolpert et al., 1998). The forward model is thought to be part of the internal feedback system controlling the on-going trajectory of the eye during saccades. However, by computing the predicted sensory consequences of a movement the forward model is also a good candidate for contributing to the computation of the error signal driving adaptation. This idea is supported by the study of cerebellar human patients in whom SA is impaired (Straube et al., 2001; Alahyane et al., 2008; Panouillères et al., 2013a), of healthy humans using neuroimaging (Gerardin et al., 2012; Desmurget et al., 1998; Blurton et al., 2012) or TMS/tDCS (Jenkinson and Miall, 2010; Panouillères et al., 2015), and finally by monkey lesion or electrophysiological studies (Takagi et al., 1998; Robinson et al., 2002; Catz et al., 2005; Catz et al., 2008). In this view, the cerebellum would implement the forward model which would send out a prediction signal to upstream structures which would compare it to the actual sensory consequences. The discrepancy between the two results in an error signal. Note however, that this does not exclude that the cerebellum could compute the error signal itself and could send it to the SC, since it also receives information about the sensory consequences of the movement. The error signal is then used to drive the adaptation, *i.e.* the change in motor command.

The SC has been postulated to operate this change in target representation since both visual and motor representation co-exist in the intermediate of that structure. However, as stated in the introduction, data on the involvement of the SC in SA are controversial. Furthermore, and even more significantly, if target representation changes uniquely at the level of the SC, SA processes would be restricted to the common final part of the saccadic circuitry. This is in absolute contradiction with the different mechanisms observed for VS and RS adaptation as well as for the forward and backward adaptation. This would also be incompatible with the involvement of cortical areas in SA mechanisms which has been reported by several studies (reviewed in the State of the art).

Two different cortical areas could be involved in adaptation-related updating of visual representation: (1) the parietal cortex (*e.g.* IPS) and (2) the frontal cortex (*e.g.* FEF). The FEF contains maps of visual and motor space (Bruce and Goldberg, 1985). Moreover, it is connected to the cerebellum *via* the ventro-lateral nucleus of the thalamus (VL) and it has been demonstrated that the disruption of this pathway in patients with thalamic lesion impairs SA (Gaymard et al., 2001; Zimmermann et al., 2015). Concerning the parietal cortex, it also contains visual representations of the external world and has direct connection with the visual areas which provide the actual consequences of saccadic eye movements. Finally, the parietal cortex and the FEF are both part of the dorsal attentional network and are highly connected *via* the SLF.

The forward model transmits to the cerebral cortex information about the ongoing adaptation processes. Therefore, it is a good candidate to initiate the functional coupling observed at the cortical level for both VS and RS regardless whether the mechanisms subtending them are different or not. However, contrary to our results, this hypothesis predicts non specific effects on attention of the various forms of saccadic adaptations (leftward and rightward saccades, backward and forward ISS).

2.2.1.2. Corollary discharge

The corollary discharge encodes the size and the direction of an upcoming movement. One pathway providing the eye movement CD to the cortex emerges from the SC and reaches the FEF *via* the Mediodorsal nucleus of the thalamus as identified in both human (Ostendorf et al., 2010) and monkeys (Cavanaugh et al., 2016b). The lesion of this pathway leads to an impairment in coding the eye position after an eye movement. The CD is modified during adaptation so as to accurately encode the actual saccade amplitude and not the sensory vector eliciting it (Collins, 2010). However, according to Zimmermann and Lappe (2016), it is possible that the system relies on several CDs from different neural structures. For example, the CD from the cerebellum could be accurate regarding the motor command while the CD emitted by the SC would encode the intended saccade (the sensory vector eliciting the saccade). These authors postulated that the mislocalization effect results from the discrepancy between the updated visual space representations and the CD coding for sensory vector in the SC that is not (yet) modified by adaptation.

The CD, as an accurate estimate of the movement, plays a role in localization. However, its role in the boosting effect is unclear, unless the boosting effect relies on visual remapping of space as suggested for VS adaptation.

2.2.1.3. Conclusion on VS adaptation effect

At the systemic level

In our own research, we were interested in the effect of VS adaptation on endogenous orienting of attention. We postulated in the section on the Difference between adaptation types (2.1) that the boosting effect could emerge from an SA-induced compression of space centered on the fovea resulting from the updating of the visual space.

In this framework, we could postulate that the CD coding for the actual movement (probably emerging from the cerebellum) is also sent to the parietal cortex. Indeed, Prevosto et al. (2010) reported that the cerebellum and the parietal cortex are connected *via* the thalamus.

Furthermore, data reported by Colby et al. (1995) showed that neurons in the monkey LIP (homologue of the human PEF) are remapped in conjunction with saccades. VS adaptation would act on the orienting of endogenous attention at the level of the PPC for the following reasons (Figure 44):

- The disruption of the right posterior IPS and not the left posterior IPS nor the right FEF increased alpha synchronization in both left and right visual cortices (Capotosto et al., 2009; Capotosto et al., 2012; Ruff et al., 2008; Ruff et al., 2009).
- The mislocalization effect due to a mismatch between the CD from the SC and the CD from the cerebellum occurs at the level of the FEF according to Zimmermann and Lappe (2016). This mismatch involves that the updating of the visual space has not yet been achieved. Since the boosting effect of VS adaptation is supposed to involve the updating of the visual space, we think it should not take place at the FEF.

General discussion

- The PPC contains priority maps on which the remapping due to SA could act and then in turn impact endogenous orienting (Bisley and Goldberg, 2010).

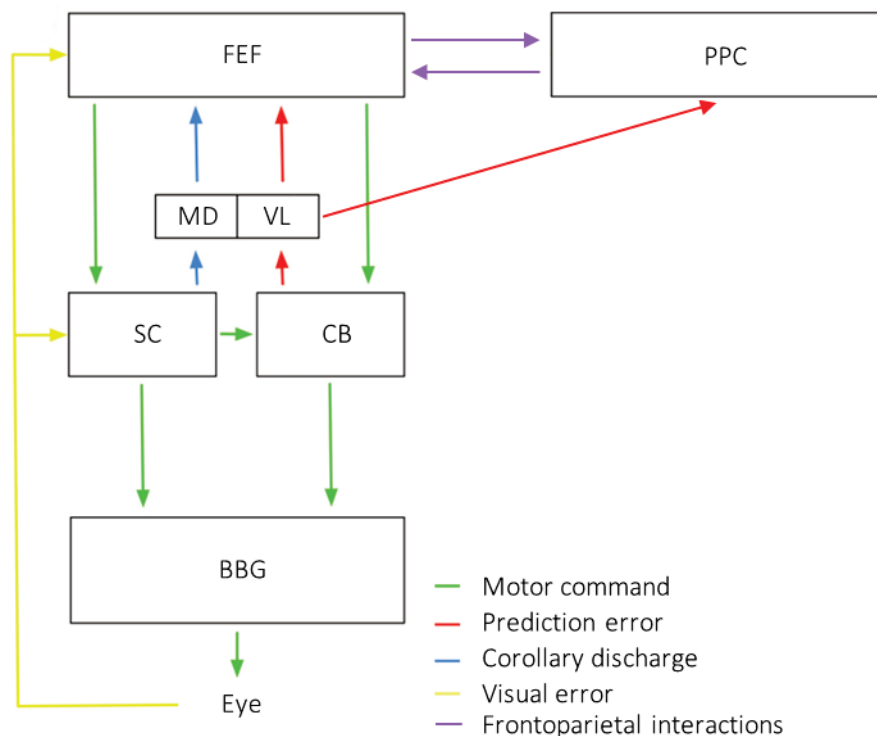


Figure 44: Proposed cortical and subcortical interactions in updating of the visual space (modified from Zimmermann and Lappe, 2016). The Frontal Eye Field (FEF) sends a motor command to the Superior Colliculus (SC) and to the Cerebellum (CB). Both SC and Cerebellum sends the motor command to the Brainstem Burst Generator (BBG) which in turn will control the extraocular muscles. The FEF receives feedback from the SC via the mediodorsal nucleus of the thalamus (MD) and from the cerebellum via the ventrolateral nucleus of the thalamus (Zimmermann and Lappe, 2016). Here we suggest that the Cerebellum also sends feedback to the posterior parietal cortex (PPC) via the thalamus (probably via VL).

At the neuronal level

At the neuronal level, the priority map hypothesis proposed by Bisley (2011) predicts that each space point is represented by a baseline activity. During updating of the visual space representation in an oculocentric frame of reference, the compression of space will shift activity from more eccentric space points towards the fovea. Therefore, the closer the targets from the fovea, the more it will benefit from the shift of activity of other, more eccentric, space points. The activity of peri-foveal space points therefore increases. It has been shown that the activity predicts the shifting time of covert attention (Bisley and Goldberg, 2003; Bisley and Goldberg, 2006). However, this hypothesis predicts also that once the remapping has been done, the boost of orienting of attention would disappear since the priority map would have been normalized.

What if

Several arguments can be raised against this prediction. First, compression of space is observed at the position of the saccade target during the adaptation exposure even in ocular fixation conditions as it

was the case in all of our studies. Yet, our results for VS adaptation showed that the orienting towards the 7.5° targets was not impacted by SA. Second, compression of space after backward adaptation predicts that mislocalizations are observed in the direction of the adaptation and in the hemifield of the adapted saccade. This is in direct opposition to our results showing that leftward VS adaptation boosts orienting toward the two hemifields. Furthermore, the visual representation maps are parametric, therefore, the shift induced by the backward adaptation of leftward VS saccades should have shifted the representation of the target further away from the fovea in the right hemifield and we should have observed no effect or even a decreasing effect on the orienting towards the right hemifield, which is not the case. Finally, the updating of the visual space as being responsible for VS boosting effect would involve that there are two different mechanisms at work for VS and RS adaptation boosting effects, which is not a parsimonious explanation.

Instead of having different mechanisms for the boosting effect of VS and RS adaptation, we actually believe that the results observed in the voluntary/endogenous modality can be explained by the same mechanisms as for the reactive/exogenous modality.

2.2.2. Increased excitability of the network

In this section we will first introduce the interhemispheric imbalance theory in the framework of prismatic adaptation and then, based on this, we will propose a new framework to interpret the results obtained with SA during this PhD.

2.2.2.1. Interhemispheric imbalance

The theory of the interhemispheric imbalance states that the left and right PPC exert reciprocal inhibition but that an asymmetry exists in favor of the left hemisphere according to Kinsbourne (1977). Nowadays, it is well established that this imbalance is actually in favor of the right hemisphere (Heilman and van den Abell, 1980; Mesulam, 1981; Cohen et al., 1994; Corbetta et al., 2005; Pisella et al., 2005).

Pisella et al. (2005) proposed that PA, another well-established model of visuo-motor plasticity, relies on the cerebellum and affects cognition. PA remotely shift vision rightward or leftward. In Pisella et al.'s (2005) model, the cerebellum ipsilateral to the deviation first inhibits the posterior parietal cortex contralateral to the prismatic deviation which will in turn affect spatial cognition. In other words, rightward PA would impact the right cerebellum which will in turn exert an inhibition on the left PPC, biasing attentional orientation towards the left hemifield due to a release of IHI on the right PPC (Figure 45, left panel). Indeed, (1) neglect is predominant after a right PPC stroke and rightward PA is known to ameliorate neglect symptoms (Rossetti et al., 1998) and (2) leftward PA induces neglect-like behavior in healthy subjects (orienting bias towards the right hemifield) while rightward PA has no effect (Colent et al., 2000; Schintu et al., 2014). Finally, it has recently been demonstrated that, in healthy subjects, leftward PA has an impact on the excitability of the left PPC-M1 tract through inhibition of the right PPC. Rightward PA has no effect on PPC-M1 excitability (Martin-Arévalo et al., 2016b). Leftward PA also has an impact on electrophysiological markers of attention (Martin-Arévalo et al., 2016a). These latter results suggest that the right PPC exerts a greater inhibition on the left PPC than the other way around. They also account for the fact that rightward PA benefits to neglect patients by inhibiting the intact left

General discussion

PPC thus re-establishing the balance between the two PPC and reducing the hyper-excitability of the PPC-M1 tract in the left hemisphere observed in these patients (Koch et al., 2008).

Saj et al. (2013) measured BOLD activation in neglect patients before and after rightward PA. They found that after PA, the activation of the SPL and the MFG increased bilaterally. They suggested that this bilateral recruitment of fronto-parietal networks may counteract the pathological biases produced by right hemisphere damage, and re-establish the balance between the two hemispheres. The inhibition of the left PPC through rightward PA will turn into a release of inhibition on the right PPC modifying the IHI and restoring a symmetrical excitability of the two fronto-parietal networks. This IHI has been proposed to be underpinned by the inhibitory neurotransmitter γ -Aminobutyric acid (GABA) (Chen, 2004), which is also thought to be involved in generating gamma oscillations (see for review: Bartos et al., 2007).

After rightward PA in neglect patients, the sustained phase of adaptation (corresponding to spatial re-alignment) has been associated with a modulation of activity in bilateral superior temporal sulcus (Luauté et al., 2006). Striemer and Danckert (2007) postulated that rightward PA might primarily modulate cortical activity *via* correction signals from the right cerebellum to the left SPL/IPS, and subsequently influence spatial neglect through callosal connections from left to right SPL which would enable the leftward re-alignment signals processed in left parietal cortex to be transmitted to right hemispheric areas that are normally responsible for orienting leftwards. This hypothesis is consistent with imaging results in healthy subjects (Danckert et al., 2008; Luauté et al., 2006) showing that both the bilateral SPL and the right cerebellum are activated during the adaptation phase with leftward PA.

The literature about PA has provided a good amount of evidence for a dominance of the right hemisphere in orienting of attention especially in the exogenous modality. However, this dominance might also hold true in the endogenous orienting as suggested, among others, by Duecker and Sack (2015). They postulated that the dorsal and the ventral fronto-parietal networks are both under right dominance and that this dominance is already present at the level of the FEF.

PA and SA, although different, have shared mechanisms since they both rely on (1) the mismatch between the CD of the movement and the predicted consequences of the movement (forward model) producing an error signal emerging from either the stepped target (SA) or the vision shift (PA); (2) the progressive change of the relationship between the sensory vector and the motor vector; and (3) the re-alignment of space subsequent to this adaptation.

2.2.2.2. Conclusion on saccadic adaptation effect

Contrary to what we initially suggested, we come to propose that the mechanisms subtending the boosting effect in the reactive/exogenous and in the voluntary/endogenous modalities are similar yet relying on different neural substrates.

At the systemic level

Our proposal relies on the interactions between the IPS, the right TPJ and the visual cortices (Figure 45, left panel). This proposal will try to show that the exposure to saccadic adaptation modifies these interactions and results in the observed boosting effects. From now on, saccadic adaptation will refer

to the backward adaptation of leftward saccades unless further specified. Our proposal postulates that these interaction modulations are a consequence of SA process. Therefore, we will not develop on the origin of SA *per se* and notably on the known involvement of subcortical structures such as the SC or the BBG.

SA acts on these interactions initially *via* signals sent from the cerebellum (Figure 45, right panel). We suggest that the cerebellum reports the encoding of the error signal and the direction of the adapted saccades differently to the cerebral cortex (referred to as the error signal and the saccade signal respectively from now on). The interactions between the cerebellum and the cerebral cortex during SA have been reported in two studies as far as we know (Zimmermann et al., 2015; Gaymard et al., 2001). However the nature of these interactions have not been investigated, therefore we will postulate a dual effect of the cerebellum on the cerebral cortex emerging from the two different signals presented above:

- From the PA literature, we extrapolate that the cerebellum, encoding the ipsilateral error signal, sends inhibiting projections (Striemer and Danckert, 2007) to the contralateral IPS *via* the VL. In leftward backward SA, the error signal is rightward and underpinned by the right cerebellum. This latter will thence inhibit the left IPS.
- From the PA literature again, we know that PA also recruits the contralateral hemisphere of the cerebellum in healthy subjects (Danckert et al., 2008; Luauté et al., 2006). However, the origin of this activation is not clear and we propose that in SA, it comes from the saccade signal. In the present case, this signal is leftward and is encoded by the left hemisphere of the cerebellum. We propose that saccade signal is reported to the right PPC *via* the VL as activating signals. Although the recalibration of the visual space has been rejected as responsible for the boosting effect observed here, we can postulate that the saccade signal sent from the cerebellum to the contralateral PPC is used for the recalibration of the visual space needed after any type of oculomotor plasticity.

The idea of different cerebellar signals transmitted to the cerebral cortex needs stronger substantial evidence. However, Catz et al. (2005) reported in their study the complex spike pattern of Purkinje cells that were selected for their preferred saccade direction. Their initial hypothesis was that the discharge will be maximal at the beginning of adaptation and will diminish along with the error during adaptation. Contrary to that, their results showed that the discharge increased and reached its maximum when the adaptation reached the classical asymptote from which no further gain change is observed. These results suggest that the error signal (Herzfeld et al., 2014) and the saccade signal (Catz et al., 2005) are encoded differently during the adaptive process. Another possibility is that the nature of the signal sent by the cerebellum is equivalent and, in function of the cerebral region reached, it will lead to different brain responses. For example, the direction of the adapted saccade informs about the part of space that has to be recalibrated and therefore the contralateral hemisphere launches plasticity processes and increases its brain excitability. Conversely, the error signal has to be minimized. This can be achieved by two strategies, either changing the motor command or changing the tolerance to the error signal. These two processes are not exclusive, and the latter can also account for the incomplete gain changes observed when the asymptote is reached during SA exposure. Minimization of the error signal could emerge from an inhibition sent to cerebral cortex encoding this input.

Yet, while still an assumption we will consider that the left cerebellum activates the right PPC and increases its brain excitability. The RS adaptation increases brain excitability at the level of the right TPJ while the VS adaptation increases the brain excitability at the level of the right IPS (Gerardin et al., 2012). The fact that the modulation of different cortical areas by different adaptation types is supported by the segregated substrates subtending them already at the level of the cerebellum (Alahyane et al., 2008).

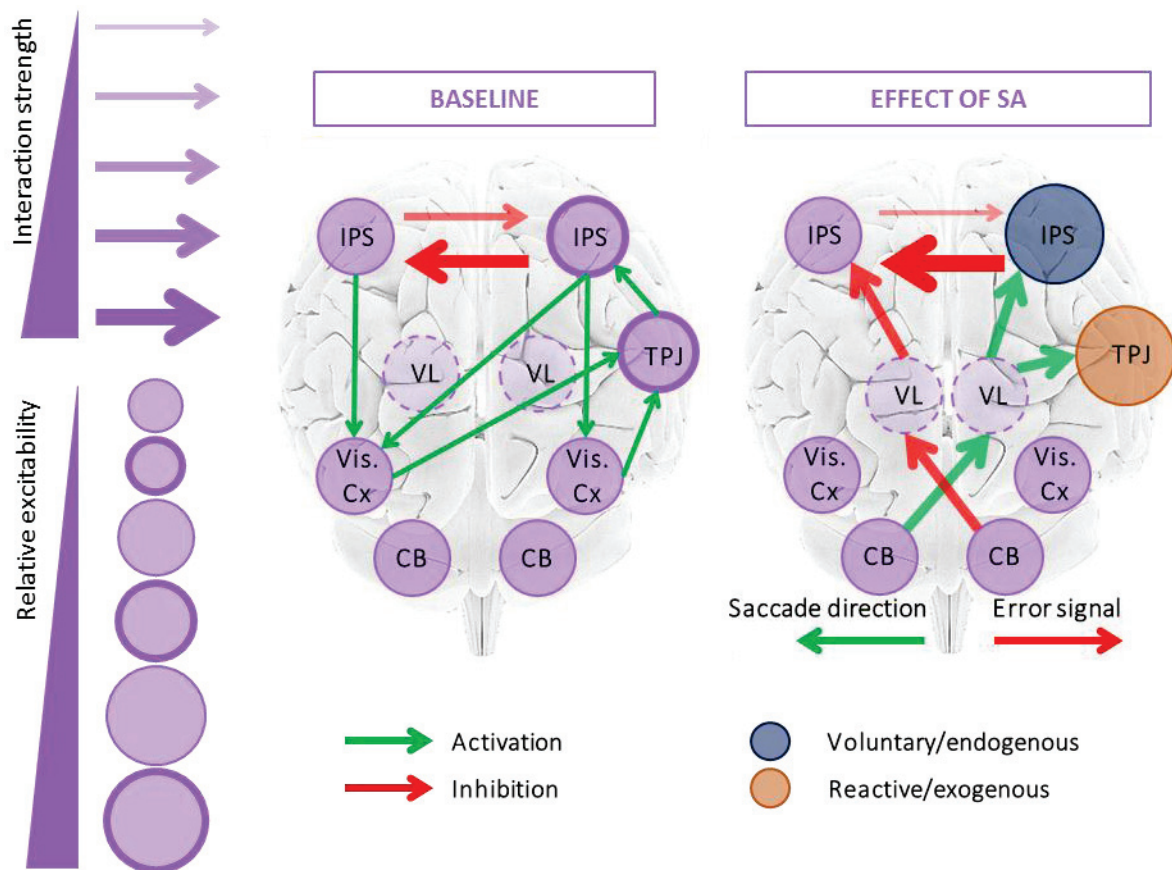
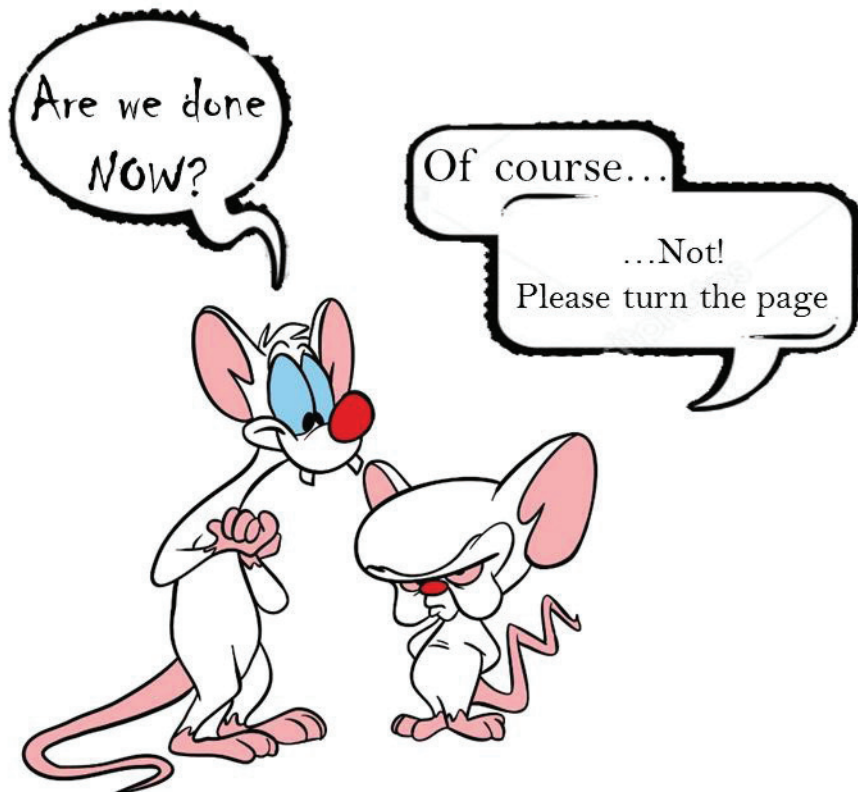


Figure 45: Interactions involved in backward adaptation of leftward saccades. *Left panel:* baseline interactions before Saccadic Adaptation (SA). The left Intra-Parietal Sulcus (IPS) sends top-down signals to the left visual cortex (Vis. Cx). The right IPS sends top-down signals to the right and the left visual cortices. The right Temporo-Parietal Junction (TPJ) receives bottom-up sensory inputs from both visual cortices and acts as a circuit breaker on the right IPS. The two IPS exert unbalanced reciprocal inhibition in favor of the right IPS. *Right panel:* Changes produced by SA. The rightward error signal activates the right hemisphere of the cerebellum (CB) which in turn inhibits the left IPS. Simultaneously a saccade signal is encoded ipsilaterally by the left CB and activates either the right IPS in case of voluntary SA or the right TPJ in case of reactive SA. The imbalance between the right and the left IPS is further enhanced by the activation of the right IPS and the inhibition of the left IPS resulting from SA.



Voluntary/endogenous modality (Figure 46).

Before voluntary SA (Figure 46, upper panel). In the context of an endogenous attentional orienting task (Figure 46A), the two IPS send top-down signals to the visual cortices to modulate their excitability and therefore their readiness to process an upcoming stimulus. The top-down signals from the contralateral IPS result in an alpha desynchronization in the contralateral visual cortex; while reduced top-down signals from the ipsilateral IPS results in an alpha synchronization in the ipsilateral visual cortex. The left IPS sends top-down signals to the left visual cortex (Figure 46B) while the right IPS sends signals to the right and left visual cortices (Figure 46C) (Capotosto et al., 2009; Capotosto et al., 2012).

After voluntary SA (Figure 46, lower panel). The right IPS is activated *via* signals coming from the left hemisphere of the cerebellum. Simultaneously, the left IPS is inhibited by error signals arising from the right hemisphere of the cerebellum (Figure 46D). The inhibition exerted by the left IPS on the right IPS is thus weaker, further enhancing the right IPS activation. The boosting effect observed for both hemifields in an endogenous attentional orienting task can be explained by the following considerations. When the cue points toward the left (Figure 46E), the right IPS is activated. Yet, the baseline activity of the right IPS has been enhanced by SA as mentioned above. The processing in the right visual cortex of stimuli in the left hemifield is thus enhanced. When the cue points toward the right (Figure 46F), both IPS are activated. As previously mentioned, the left IPS is activated for contralateral cues and the right IPS is activated for both ipsilateral and contralateral cues. The modulation of the right visual cortex by the left IPS is weaker due to the inhibition exerted by the right cerebellum. Yet, the left visual cortex benefits from the hyper activation of the right IPS and the processing of rightward upcoming stimuli is enhanced. Our results also highlighted that the boosting effect was restricted to shifts occurring for 3° of eccentricity targets. In our proposal, that would involve that the increased activity of the IPS is centered on the fovea which is in accordance with the oculocentric representation of visual space in the PPC (Colby et al., 1995).

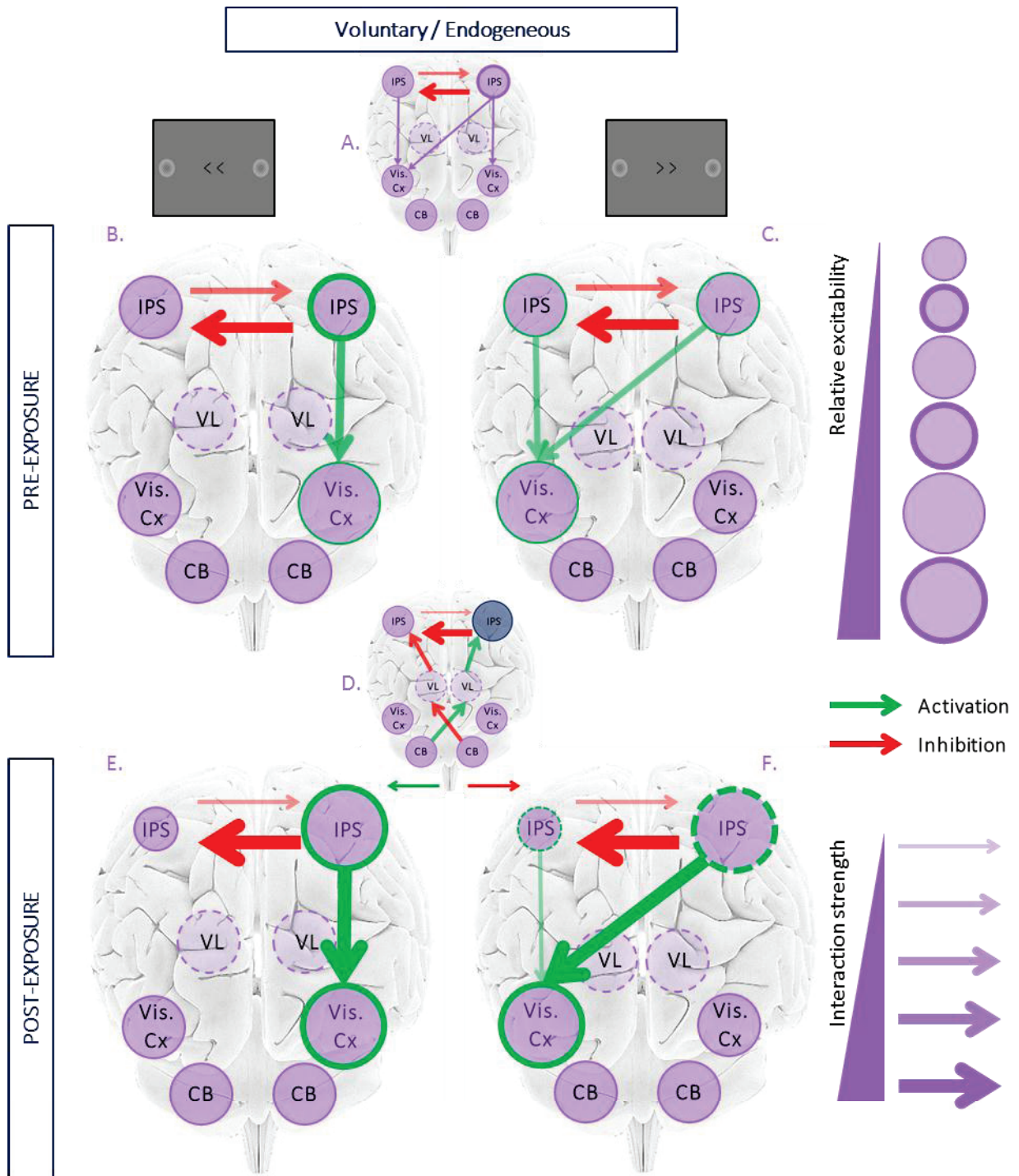


Figure 46: Interactions involved in the coupling in the voluntary/endogenous modality. **Upper panel:** Before the exposure to backward adaptation of leftward VS. **A:** See legend Figure 45, left panel. **B:** When the cue points towards the left hemifield, the right, contralateral, Intraparietal Sulcus (IPS) is activated and sends top-down signals to the right, contralateral, visual cortex (Vis. Cx) to modulate its excitability. **C:** When the cue points towards the right hemifield, the left, contralateral, and the right, ipsilateral, IPS are activated. They both equally contribute to the top-down signals sent to the left visual cortex which modulate its excitability. **Lower panel:** After the exposure to backward adaptation of leftward VS. **D:** See legend Figure 45, right panel. **E:** In case of the leftward cues, the right IPS is therefore hyper activated and further increases excitability in the right visual cortex. **F:** In case of rightward cues, the left IPS is weakened by the right CB however, the hyper-excitability of the right IPS compensates and increases excitability in the left visual cortex.

Reactive/exogenous modality (Figure 47)

Before reactive SA (Figure 47, upper panel). When an unpredicted, exogenous, signals arrives in the visual field, the visual cortices send bottom-up signal to the right TPJ. The right TPJ acts as a circuit breaker of the dorsal attentional network through common prefrontal areas (not represented on the scheme) (Corbetta et al., 2008) (Figure 47A). Eventually, the breaking signal activates the right IPS in case of attentional capture in the left hemifield (Figure 47B). Whether this signal reaches first the FEF before reaching the IPS is not considered in the following conclusion since our data do not provide sufficient material to make any prediction. Yet, when the attentional capture occurs in the right hemifield, the right TPJ sends inhibitory signals to the right IPS which will thus release its inhibition on the left IPS. The left IPS is thus activated (Figure 47C). The IPS modulates in turn the respective visual cortex with top-down signals. The balance between the alpha desynchronization in relevant sensory areas and synchronization in irrelevant ones results from the inter-hemispheric inhibition already at the level of the IPS.

After reactive SA (Figure 47, lower panel). After reactive SA, the right TPJ is hyper activated (from the left cerebellum encoding the direction of the saccade) while the left IPS is inhibited (from the right cerebellum encoding the error signal) (Figure 47D). In this modality, we observed that the boosting effect is hemifield specific, restricted to the left, but the targets of all eccentricities tested benefited from the boosting effect. When the cue is flashed in the left hemisphere (Figure 47E), the hyper activated right TPJ sends stronger signals to the right IPS. Moreover, since the left IPS is inhibited, the right IPS has already its baseline activity increased. The right IPS modulates the right visual cortex more efficiently and the processing of targets in the left hemifield is enhanced. When the cue is flashed rightward (Figure 47F), the right TPJ sends inhibiting signals to the right IPS. The inhibition from the right to the left IPS is thence decreased. Yet, the left IPS is inhibited by the right cerebellum. The inhibition and the increased activation are cancelling out. The result is that the benefit of the cue is still observed but the orienting is not further boosted by SA.

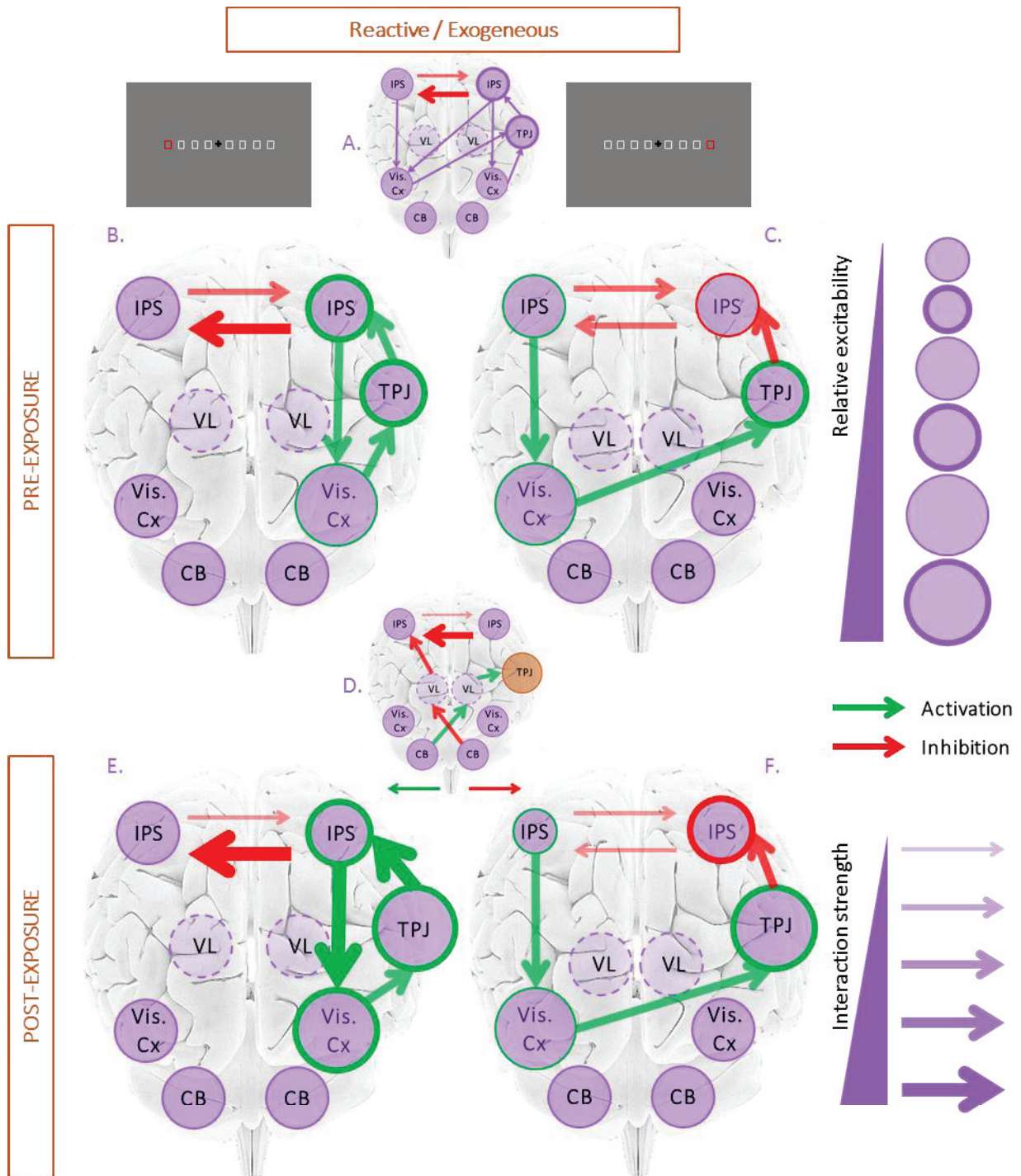


Figure 47: Interactions involved in the coupling in the reactive/exogenous modality. *Upper panel:* Before the exposure to backward adaptation of leftward RS. **A:** See legend Figure 45, left pannel. **B:** When the cue flashes in the left hemifield (left panel), the right Temporo-Parietal Junction (TPJ) is activated and sends activating breaking signals to the right Intraparietal Sulcus (IPS), which in turns sends top-down signals to the right visual cortex (Vis. Cx) to increase its excitability. **C:** When the cue flashes in the right hemifield (right panel), the right TPJ sends inhibiting breaking signals to the right IPS which releases inhibition on the left IPS. The left IPS is therefore activated and sends top-down signals to the left visual cortex. **Lower panel:** After the exposure to backward adaptation of leftward RS. **D:** See legend Figure 45, right pannel. **E:** In case of a cue flashed in the left hemifield, the right TPJ is hyper-activated and sends stronger breaking signals to the right IPS, which in turns sends stronger top-down signals to the right visual cortex (Visual Cx). **F:** In case of a cue flashed in the right hemifield, the right TPJ sends stronger breaking signals to the right IPS which releases even more its inhibition on the left IPS. However, the left IPS is weakened by the signal from the right hemisphere of the CB, therefore, no difference between before and after SA is observed at the level of the left visual cortex.

Absence of effect after rightward adaptation (Figure 48)

In case of rightward backward adaptation, the error signal from the left cerebellum would inhibit the right IPS and the saccade signal from the right cerebellum would activate the left hemisphere. However, the TPJ of the left hemisphere is not involved in the capture of attention (Corbetta et al., 2008). Therefore, in case of RS adaptation, its increase of excitability does not affect performance in an attentional task.

In case of VS adaptation, again, the left IPS would be activated and would thus more strongly inhibit the right IPS, weakening the activity of the latter. In addition, the right IPS is also inhibited by the left hemisphere of the cerebellum (leftward error signal). As a consequence, the activity of the left and right IPS would be equivalent instead of being in favor of the right IPS. When the cue is leftward, the right IPS would be activated. However, the right IPS activity is decreased in contrast to before SA as described. The cue benefit could be the same or even decreased. Our results suggest that the cue benefit is not impaired suggesting that the activity of the right IPS remains sufficient to send top-down signals to increase the excitability of the left visual cortex. When the cue is rightward, the left and the right IPS are activated. The weaker activation of the right IPS is compensated by the stronger activation of the left IPS. Therefore, the cue benefit is equivalent as before adaptation from the same top-down signals sent from the two IPS.

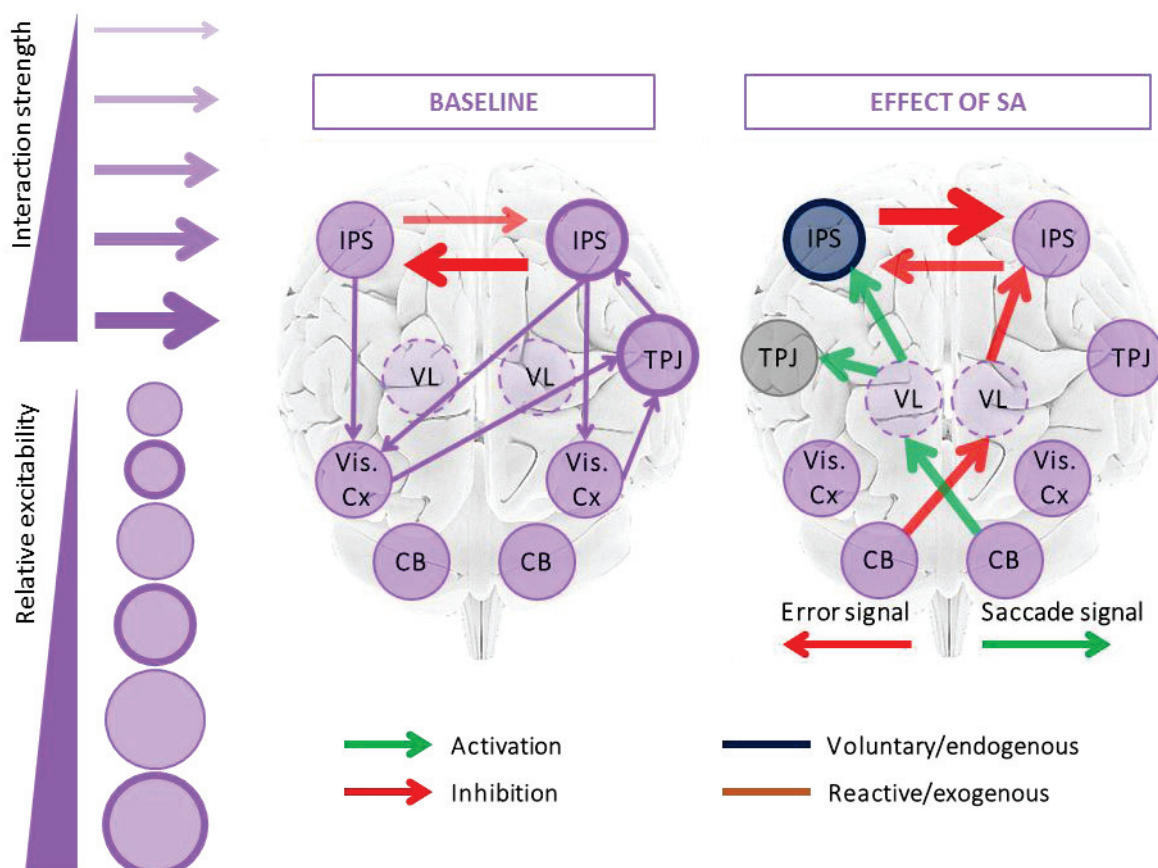


Figure 48: Interactions modulation after rightward backward saccadic adaptation (SA). *Left panel:* See legend Figure 45, left panel. *Right panel:* Changes produced by rightward SA. The leftward error signal activates the left hemisphere of the cerebellum (CB) which in turn inhibits the right IPS. The rightward saccade signal is encoded ipsilaterally by the right CB and activates the left TPJ in case of reactive SA. However, the left TPJ is not involved in the orienting of attention, therefore no effect would be observed. In case of voluntary SA, the left IPS is activated and the right IPS, initially dominant, is inhibited. This results in an equal activation between the left and right IPS and the cue benefit is equivalent as before SA.

Absence of effect after forward adaptation

Regardless of the modality tested or of the direction of the adapted saccade, forward adaptation of saccades would lead to the error signal and the saccade signal having similar direction. The same hemisphere of the cerebellum would be activated by these two components of SA. The inhibition and activation signals would be sent to the same cerebral hemisphere. The result of these inversed modulations would be null and consistently our results showed, at least for RS adaptation, that forward adaptation did not produce a boosting effect.

At the neuronal level

At the cellular level, GBA has the basic properties to represent a precise temporal framework for synaptic plasticity in terms of long-term potentiation and depression (Traub et al., 1998). A growing body of evidence suggests that GBA is a good candidate for supporting plasticity in numerous forms. GBA supports the maintenance of information during working memory tasks (Haegens et al., 2009). In this study, they asked subjects to perform a frequency discrimination between two subsequent tactile stimuli. They found that GBA increased during the entire duration of the retention phase bilaterally in the secondary somatosensory cortex. In another modality closer to our paradigm, Perfetti et al. (2011) showed that GBA increased after a visuo-manual learning task over the right parietal cortex. Medendorp et al. (2007) used a delayed double-step saccade task to show that GBA increases during the delay between the appearance of the target and the subsequent saccade. Interestingly, in their spatial working memory task involving delayed saccades, the GBA regain in intensity just before the movement. This suggests that GBA might link the sensory vectors encoded in the memory and the motor vectors, allowing the eyes to successively target these two remembered locations. These findings are in line with those of Van Der Werf et al.'s (2008) study in which pro- and anti-saccade tasks were used to disentangle the sensory vector and the motor vector (respectively stimulus and goal component with their words) in the GBA. They found that while the sensory vector is coded by a transient activity in occipital regions, the motor vector is coded by a sustained activity around the contralateral IPS.

Moreover, it has been extensively demonstrated that good behavioral performance is associated with either post-stimulus GBA evoked intensity or pre-stimulus ongoing GBA (*e.g.* Hoogenboom et al., 2010; for review: Fries et al., 2001; Jensen et al., 2007; Tallon-Baudry and Bertrand, 1999). GBA has been causally related to increased performances in a neurofeedback study. Subjects trained to increase the GBA were tested before and after such training phase in a perceptual task. The authors reported a subsequent beneficial effect of the GBA increase on perceptual performances (Salari et al., 2014).

At the level of the visual cortex, we can predict from the literature that the boosting effect could be reflected as alpha desynchronization in the contralateral cortex and alpha synchronization in the ipsilateral cortex. However, it does not seem reasonable that at the level of the IPS the increase of GBA modulates alpha rhythms remotely in down-stream areas such as the visual cortices.

We propose that GBA would increase locally at the level of the IPS prior the transmission of IPS top-down signal to the visual cortex³. The directional communication (from IPS to downstream regions such

³ The logical consequence of this assumption is that GBA would modulate alpha rhythm at the level of the IPS. However, this conclusion is not, to my knowledge, supported by empirical evidence (yet).

as the visual cortex), would be mediated by the alpha rhythm that has been shown to be involved in top-down flow of information.

2.3. Wrapping it up

This PhD work aimed at disclosing the functional coupling between saccadic adaptation and attention. These two processes, indeed, share segregated neural substrates in the fronto-parietal network of attention. Adaptation of voluntary saccades involves the dorsal attentional network; whereas reactive saccades adaptation implicates the ventral attentional network. This body of evidence led us to investigate the neurophysiological basis of the coupling in the reactive/exogenous modality and to further behaviourally characterize this coupling in both the reactive/exogenous and voluntary/endogenous modalities. We therefore conducted an MEG study which was the first to record brain electrophysiological signals during and after saccadic adaptation. The results showed that adaptation process increases gamma band activity. Interestingly, this increase was sustained in the subsequent attentional task and found in wide network including the posterior part of ventral fronto-parietal network. These two findings make the gamma rhythm a good candidate as neural underpinnings of the coupling between adaptation and attention.

Attention and saccadic adaptation also impact each other. In this PhD work, we confirmed these previously reported results and further showed that adaptation of leftward reactive saccades increases the benefit from exogenous cues in orienting attention. Our work also revealed that this holds true for the voluntary/endogenous modality as well. Interestingly, we showed that only leftward, but not rightward adaptation boosts orienting of attention. Furthermore, we showed in the reactive/exogenous modality that this effect was restricted to the backward adaptation (leading to a decrease of saccadic amplitude). According to our model, we suggest that forward adaptation of voluntary saccades as well, would not benefit to the endogenous orienting of attention.

The results accumulated during this PhD allowed us to propose a comprehensive model of SA and of the coupling between SA and attention. This model is the first to provide a description of the dynamical interactions between cortical areas and the cerebellum likely involved in the coupling between attention and saccadic adaptation. This model is compatible with the attentional literature and also the literature on the functional consequences of another type of adaptation: PA. It also is in agreement with the sparse literature on the cortical activity modulated by saccadic adaptation.

We propose that the neural substrates shared between attention and adaptation are not only overlapping at the macroscopic level but are also hosting neuronal populations co-activated for saccades and attention. Namely, oculomotor plasticity modulations of the cortical activity leaks into the overt and covert attentional networks. SA signals sent by the cerebellum activate the common neural substrates, including priority maps, used both by attention and eye movements to select targets, and this activation is reflected by an increase of GBA. These signals also biased the interhemispheric imbalance between the left and right posterior parietal cortices.

This PhD work also provides further evidence for common priority maps for attention and eye movements which may have been implemented in the course of natural selection due to its advantage in terms of neural resource. Finally, this model provides strong predictions for further research.

3. To infinity, and beyond!

In this section, we will have the privilege to be out of space, time, and money dimensions! Therefore, we will use this opportunity to expose the main experiments we could/should further execute to complement the present work and deepen our understanding on the link between oculomotor plasticity and attention.

3.1. Basic perspectives

3.1.1. Further Behavioral studies required

In this section we will propose experiments to tackle the pending questions beyond the limits of this PhD work. A potential question could have addressed the possible generalization to other oculomotor behaviors of the boosting effect highlighted in this PhD work. It would be interesting to know whether other types of eye movement plasticity induce benefits to other cognitive processes. For example, the plasticity of vestibulo-ocular reflex could act on body representations. However we will limit this section to the perspectives concerning saccadic adaptation.

3.1.1.1. Look the other way

In our main hypothesis, we posited that the coupling between attention and SA is bidirectional. Therefore, to further complete this work, one (me?) should test the prediction of the effect of attention on SA. Gerardin et al. (2015) already tested the effect of increasing the attentional load during SA and showed that it positively increased SA efficiency. However, in this paradigm, the two tasks were simultaneous. To test the existence of a coupling supported by a sustained increase of brain excitability, the attentional task and the SA exposure should be separate in time and the orienting task should precede the SA procedure. One potential design would involve sessions with increasing recruitment of attentional networks and test its impact on SA efficiency. For example, one session could involve only uninformative trials, another 50% of informative and 50 % of uninformative trials and finally, a third session with 100% of informative trials. We predict that SA efficiency will increase with an enhanced involvement of attention in the preceding task.

3.1.1.2. On the extent of the boosting effect

In our experiment investigating RS adaptation, the boosting effect was observed for the entire hemifield. Therefore, we can predict that adapting a saccade of a different amplitude than the amplitude we adapted (11°) would yield a similar effect. Moreover, since we proposed that the increased excitability of the right TPJ acts on the breaking circuit through the right IPS, it sounds reasonable to predict that this effect should concern the entire hemifield regardless of the adapted saccade amplitude. Conversely, in the voluntary/endogenous modality, we found that adapting saccades of 11° had a spatially restricted effect at 3° of eccentricity. It could be interesting to adapt larger saccades and observe the effect on other target eccentricities. If the observed effect remains at 3°, we can assume that the boosting effect on the right IPS is oculocentric and restricted to peri-foveal shift of attention. If the effect is observed for targets further away from the fovea, it is possible that cerebral visual maps play a partial role in the boosting effect of VS adaptation on endogenous orienting of attention.

General discussion

Also, to be able to know whether the field of the boosting effect follows the adaptation field, the attentional tasks should include targets located away from the horizontal meridian. The boosting effect in this case might follow a gradient in relation to the vertical component shared with adapted saccades. In other words, if the target is presented at a location with the same horizontal component, the size of boosting effect should decrease with the increase of vertical component change. Regarding changes in the horizontal component, the predictions are different for RS and VS adaptation effects. In the former case (RS), the boosting effect should not be affected by the eccentricity as long as it lies in the adapted hemifield. In the latter case (VS), the effect size should also follow a gradient in relation to the horizontal component shared with the adapted saccades, namely decrease with the increase of eccentricity as compared to the line of sight.

The effect of adapting vertical saccades should also be investigated. Wick et al.'s (2016) reported results suggesting that adapting vertical saccades has an effect on the attentional field. However, it would be interesting to test the laterality of such effect. Indeed, in their experiments, the targets of the attentional task were presented on the vertical axis. Here we propose to test targets lateralized to the left or to the right hemifields. Our predictions would be that after backward adaptation of vertical RS, orienting toward the left, but not the right, hemifield should be faster. In contrast, the adaptation of VS should benefit to orienting in the two hemifields. Finally, it would be interesting to test the direction of adaptation, namely downward or upward. It is possible that the boosting effect could be restricted to the upper or the lower part of the visual field. However according to our proposal, the spatial specificity concerns only a left and right dichotomy due to the hemispheric lateralization organization of the brain. Yet, in vertical saccadic adaptation, the error signal as well as the direction of the adapted saccade are not lateralized. In addition, mechanisms underlying vertical saccade adaptation remain unknown. Therefore, predictions based on our proposal are highly speculative.

3.1.1.3. On the different types of adaptation

We investigated the effect of forward adaptation in the reactive/exogenous modality, but not in the voluntary/endogenous modality. In this latter case, the leftward error signal elicited during forward adaptation of leftward VS would activate the left cerebellum which would in turn inhibit the right IPS while the leftward saccades would also activate the left cerebellum which would in turn activate the right IPS. The outcome should therefore be null and we should not observe a boosting effect of forward adaptation.

We also investigated the effect of backward adaptation for rightward VS but not for rightward RS. Note that Habchi et al. (2015) tested and failed to disclose any effect on attention of this RS direction, but their paradigm might have not been sensitive enough in evaluating the orienting of attention. Yet, according to our proposal, the rightward RS backward adaptation would not have any effect since the rightward saccade signal would activate the right hemisphere of the cerebellum which in turn would activate the left TPJ for which the attentional role does not have a counterpart in the left hemisphere. Moreover, the leftward error signal would activate the left cerebellum which in turn would inhibit the right TPJ which is necessary in orienting exogenous attention.

3.1.1.4. Specificity of the coupling

In our working hypotheses, we postulated that the coupling between attention and saccadic adaptation was modality specific. This involves that the RS adaptation would only act on exogenous, but not

endogenous, orienting while VS adaptation would affect endogenous, but not exogenous orienting of attention. In the current work, our paradigms do not tackle this aspect. Therefore, as a direct follow-up to this work, one should test the paradigm of exogenous orienting with the exposure to VS adaptation and *vice versa*.

Concerning the effect of VS adaptation on exogenous orienting, Habchi et al.'s (2015) first experiment involved a group of subjects adapted for leftward and rightward VS in the backward direction. The authors did not highlight an acceleration of RT in their spatial speeded discrimination task. Again, their paradigm might have not been sensitive enough to pinpoint the transfer of an inter-modality boosting effect. According to our proposed mechanisms, leftward VS backward adaptation should increase the right IPS excitability and decrease the left IPS excitability. Since the exogenous orienting of attention is supposed to be partially underpinned by the IPS, a boosting effect on exogenous orienting of attention could be observed. Moreover, this boosting effect should be restricted to the closest location from the fovea, but in the two hemifields.

Concerning the effect of RS adaptation on endogenous orienting, according to our proposal, the hyper excitability of the right TPJ could act again on the left IPS and be reflected in a boosting effect for the two hemifields. However, it is also possible that the right TPJ acts only on the right IPS when an unpredicted (invalidly-cued) target appears and therefore in case of informative (100% valid) cues, the reactive SA-induced excitability of the right TPJ would not act on the endogenous orienting of attention.

3.1.2. Further neuroimaging studies required

One assumption used in this PhD work concerns the voluntary SA-induced activation of a dorsal network reflected in the GBA. This assumption has been extrapolated from the study 1 in which we highlighted a large network including the ventral network of attention in the post-exposure saccadic task. As only RS adaptation was induced in this study, another MEG study testing specifically the coupling of voluntary SA and endogenous attention is needed. Moreover, since the extent of the network could be artefacted by the small number of trials used in the saccadic task of our study 1, one should increase it to provide a better signal-to-noise ratio. We expect to highlight a GBA increase especially in the right IPS during the post-exposure task following an exposure to SA of leftward VS as compared to a control exposure. Predictions about the GBA activity during the attentional task is harder to extrapolate from the results obtain in our study 1 because of two main reasons. First, we did not highlight a behavioral effect during this task. Second, the main GBA increase was observed in the left hemisphere. Yet, during the attentional task, the right IPS still reflected the GBA increase. These two reasons could actually be linked. Indeed, as suggested in the summary of the results (Study 1: Gamma and SA, 1.1), this GBA increase in the left hemisphere could reflect the restoration of the balance between the two hemispheres. This idea is supported by the results showing that the GBA increase in the left hemisphere is centered on the IPS. Furthermore, one can postulate that the task was too easy (high contrast of the targets), to recruit the ventral network of attention. Thus, this failure to activate the ventral network might have allowed the re-balancing of activation between the two IPS. Following this rationale, if a boosting effect of leftward VS backward adaptation on endogenous orienting is observed in this new MEG study, we predict that the increase in GBA observed during the saccadic task will persist during the attentional task in the right hemisphere at the level of the right IPS. Moreover, we predict that the alpha power in

the visual cortices of both hemispheres will be decreased as suggested by the work of (Capotosto et al., 2009; Capotosto et al., 2012).

Another important investigation concerns forward adaptation. Indeed, neuroimaging studies of SA are sparse and mostly focus on backward adaptation. Actually, to our knowledge, the only neuroimaging studies investigating forward adaptation have been reported in (Desmurget et al., 1998; Desmurget et al., 2000). These PET studies highlighted only activation of cerebellar regions. Therefore, forward SA neuroimaging studies are needed. Firstly, thanks to its spatial resolution, fMRI would provide evidence for the involvement of cortical regions and give an accurate estimate of the location of this (these) region(s). Second, a MEG study would allow to show whether forward and backward SA rely on the same increased activity (namely an increase in GBA). Indeed, because of the VS/RS dichotomy as well as of the backward/forward adaptation relying on distinct mechanisms and neural substrates, it cannot be excluded that they do not both rely on an increase in GBA. Yet, as already mentioned, GBA is a good candidate for plasticity processes thus representing a general mechanism that could underpin different processes in different brain areas.

3.1.3. Further Neurostimulation studies required

3.1.3.1. Boosting the boost

TMS studies offer the possibility to causally link neural substrates and behavioral effects. TMS can either stimulate brain areas or perturb their activity. Using TMS in our framework can be envisaged in different ways.

First, one can use TMS to stimulate brain areas during SA exposure. In the reactive/exogenous modality one could use an activating TMS procedure to stimulate the right TPJ during leftward RS backward adaptation. This stimulation could first increase SA efficiency⁴. By increasing the SA-induced plasticity, this would also enhance the slowly developing boosting effect of SA on attention highlighted in our study 2. For example, the boosting effect could be accelerated and be observed as soon as the attentional task starts (in the first block). Another possibility is that the boosting effect on the cue benefit would be larger. However, since we did not find in our study 2 a significant correlation between individual level of adaptation and cue benefit enhancement, this latter prediction is unlikely. In the voluntary/endogenous modality, stimulating the right IPS with activating rTMS could have as primary consequence an increased efficiency of SA. As secondary consequence we could observe that the boosting effect during the subsequent endogenous attentional task is increased. Yet, in study 3, the correlation between individual SA efficiency and cue benefit boost was again not significant. Therefore, this prediction might not be met because of an all-or-none effect of the SA-induced boosting effect. Another prediction would be that the boosting effect could be spatially enlarged and benefit to targets at 7.5° rather than being restricted to peri-foveal targets in study 3.

⁴ Note that a study from our laboratory (Péllisson et al., 2018) found that the spTMS over the right TPJ did not have an effect on SA efficiency. The results showed however that the retention of SA was longer after the spTMS. Therefore, the following predictions are not supported by the data of Péllisson et al.'s study. However, by using rTMS, it is possible that a boost of SA efficiency would be observed allowing the following predictions.

Second, rhythmic tACS can be used to cause entrainment of neural oscillations (Thut et al., 2011; Joundi et al., 2012). Therefore, by simulating the SA-induced GBA increase, similar behavioral effects as those observed in our studies 2 & 3 should be observed. For example, entraining GBA in the right TPJ should lead to the same boosting effect observed in our study 2. This rationale holds true in the voluntary/endogenous modality: by entraining the GBA in the right IPS, a similar boosting effect on the attentional endogenous orienting should be observed as the one reported in our study 3.

3.1.3.2. De-balancing the imbalance

In our proposal, we involved the left IPS as being inhibited by the signal sent from the cerebellum ipsilateral to the error signal. In this framework, using the disrupting effect of the TMS on the left IPS should mimic, at least in part, the effect observed in studies 2 and 3.

3.2. Rehabilitation perspectives

3.2.1. In neglect

In parallel with the work presented in this manuscript, we have launched a protocol investigating the effect of SA on attentional symptoms in neglect. Indeed, as aforementioned (see section: Dysfunction of the orienting system: neglect, a pathological model for spatial attention), PA and SA are similar processes and PA is known to be so far one of the most efficient rehabilitation procedure in neglect. We therefore think that the tight link between eye movements and attention will further enhance the benefit patients would receive from this oculomotor plasticity-induced rehabilitation (through SA).

The protocol follows Single Case Experimental Design (SCED) recommendations. SCED allows to obtain statistical power over a small and heterogeneous sample which is often the case in studies involving patients. There are several different SCED types. In this study we have chosen to multiply baseline measurements and insert the intervention (SA) after a number of repetitions randomized across patients and sessions. We decided that the principal criterion for evaluating the efficiency of our protocol is the line bisection test. Indeed, this test is easy and quick, allowing its iteration without changing the duration of the protocol significantly. Since patients will also perform a control session, we also included other tests to further evidence the benefit of SA on attentional deficits. All these tests are *pen-and-paper* classical neuropsychological tests (*e.g.* Ota test (Ota et al., 2001), Gainotti test (Gainotti et al., 1972), free drawing etc.). As in all our experiments, the design of this protocol includes a pre-exposure phase in which we first test attentional deficits and a saccadic task in which we test the baseline amplitude of saccades. Patients are then exposed to either leftward backward saccadic adaptation or control exposure. After the exposure, saccadic amplitude and then attentional deficits are retested.

The SA and control saccade exposures will be performed in the neglected hemifield, thus the saccadic task has been modified in order to facilitate the production of saccades towards this hemifield. The patients will first fixate a red upper point, then a voice will instruct them to look downward to the blue central dot. Once fixation is achieved, the central dot will disappear and simultaneously the left target will be displayed. The patient is orally instructed to look leftward. Therefore, the elicited saccades are RS in the way that the targets appears suddenly and is salient but they are also voluntary because

requiring the involvement of intern goals (following the oral instructions). The peripheral target is a moving salient stimulus to further help the capture of attention in the left, neglected, hemifield. In the backward exposure the target is displaced during the saccade while in the control exposure the target remains at the same position.

Our predictions is that the backward adaptation of leftward saccades will boost attentional performances of patients in the left hemifield. The mechanisms on which this boosting effect relies have been exposed in detail in the section (Interhemispheric imbalance, 2.2.2.1). Briefly, we believe that backward SA will restore the interhemispheric imbalance by weakening the activity of the left IPS to decrease the rightward bias (as in PA) and activate the right TPJ and the right attentional network to increase leftward orienting. The latter mechanism could be specific to SA as compared to PA and might be the source of an enhanced rehabilitating power of SA over PA.

3.2.2. Far extrapolation to other disorders

Our PhD work was focused on the plasticity of the oculomotor system, especially the saccadic system. Because of the tight link between eye movements and visuospatial attention, we hypothesized that saccadic adaptation would boost attentional performances. This PhD work has led to the proposal that this coupling results from a SA-induced increase in brain excitability. This proposal therefore suggests that different cognitive processes could benefit from this increased brain excitability. It also suggests that benefits could be observed in case of functional couplings other than the one studied here. For example, tool use and language regions overlap suggesting a functional coupling. This coupling could involve that language would benefit from tool use-induced plasticity.

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