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Cortical sources of vergence eye movements

Źródła korowe wergencyjnych ruchów oczu

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Ja, niżej podpisana

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przedkładam rozprawę doktorską

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(*Źródła korowe wergencyjnych ruchów oczu*)

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Jednocześnie przyjmuję do wiadomości, że gdyby powyższe oświadczenie okazało się nieprawdziwe, decyzja o wydaniu mi dyplomu zostanie cofnięta.

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LIST OF ABBREVIATIONS

BEM – boundary element method

BESA – Brain Electrical Source Analysis

BOLD changes – blood oxygenation level dependent changes

DLPFC – dorsolateral prefrontal cortex

EEG – electroencephalography

EOG – electrooculography

EOG_{sacc} – averaged saccade signal calculated from $hEOG_{right}$ and $hEOG_{left}$

EOG_{verg} – vergence signal calculated from $hEOG_{right}$ and $hEOG_{left}$

EPSP – excitatory postsynaptic potential

ERP – event-related potential

FDM – finite difference method

FEF – frontal eye field

FEM – finite-element method

fMRI – functional magnetic resonance imaging

GFP – global field power

$hEOG_{right}$ – horizontal EOG electrode that registered horizontal eye movements for right eye

$hEOG_{left}$ – horizontal EOG electrode that registered horizontal eye movements for left eye

ICA – independent component analysis

IPS - intra-parietal sulcus

IPSP - inhibitory postsynaptic potential

IRD - infrared reflection device

MEG – magnetoencephalography

NPC - near point of convergence

LED – light-emitting diode

OKN - optokinetic nystagmus

PCA – principal component analysis

PCC - posterior cingulate cortex

PEF - parietal eye fields

PET - positron emission tomography

PPC - posterior parietal cortex

PPRF – paramedian pontine reticular formation

pre-SMA – pre-supplementary motor area

REM sleep – rapid eye movement sleep

RMS - root-mean-square

RS – regional source

RV – residual variance

SC – superior colliculus

SEF – supplementary eye field

SMA – supplementary motor area

SSE – sum-of-square error

tDCS – transcranial direct current stimulation

TMS – transcranial magnetic stimulation

vEOG – vertical EOG electrodes that registered vertical eye movements and blinks

VEP – visual evoked potential

VOG – video-oculography

VOR – vestibuloocular reflex

V1 – primary visual cortex

V2 – secondary visual cortex

V3 – third visual cortex

ABSTRACT

In natural viewing conditions, different types of eye movements are combined since visual exploration requires performing eye movements that have both a saccadic and a vergence component (i.e., combined vergences). Saccades are conjugate eye movements that shift the eyes together in one direction whereas vergences are disjunctive eye movements, which implies that the eyes move in opposite directions. Two types of vergences can be distinguished: inward eye movements – convergences –, and outward eye movements – divergences. The presented dissertation aimed at determining the cortical areas related to the preparation and execution of combined vergences and saccades. It additionally attempted to specify the likely roles of these areas. The dissertation contains two experiments, which focus on exogenous (Chapter 2) and endogenous eye movements (Chapter 3).

The Brain Electrical Source Analysis (BESA) approach was used to investigate cortical correlates related to the preparation and execution of exogenous and endogenous combined vergences and saccades. This approach has the advantage over the event related potential (ERP) technique that it allows to determine the likely engaged cortical areas related to eye movements. Relative to functional magnetic resonance imaging (fMRI), the high temporal resolution of the approach additionally allows to determine the respective roles of the involved areas, based on a comparison of stimulus- and response-locked activities.

The first experiment focused on exogenous eye movements and revealed that three source pairs of regional sources may account for the observed ERPs, which were located within occipital cortex, frontal eye field (FEF) and anterior frontal area. However, due to the observed correlations between electrooculography signal and the frontal sources, their activity was interpreted as a residual eye movement artifact. A general preponderance of stimulus-locked activity for occipital cortex and FEF were observed, which implies that activity of both areas reflects the engagement in processes related to sensory-related processing of the stimuli that trigger the eye movements. Additionally, a greater response of both occipital cortex and FEF for combined convergences and combined divergences compared to saccades was obtained, which suggests that activity of both areas is related with processes that are characteristic for combined vergences, i.e., processing of retinal disparity. These findings appear in line with the behavioral results – latencies of eye movements, which revealed that saccades are characterized by shorter latencies compared

to combined vergences. These findings fit the conclusion that the preparation of exogenous combined vergences engages additional processes required to perform these eye movements, which might be the detection of disparity.

In the second experiment, endogenous saccades, endogenous combined convergences, and endogenous combined divergences were investigated. The results revealed (similar to the experiment on exogenous eye movements) that FEF and occipital cortex are engaged in the preparation and execution of these types of eye movements. For endogenous eye movements also the preponderance of stimulus-locked activity was observed, which emphasizes the role of these areas in processing of stimuli that trigger eye movements. Moreover, a preponderance of activity for both vergence conditions as compared to saccades was observed. As mentioned before, this preponderance may be associated with the processing of retinal disparity. Interestingly, activity within occipital cortex was the same for all eye movement types. As a consequence, it may reflect the general processing features of the presented stimuli or possibly the engagement of working memory, which seems needed to properly perform the task. For endogenous eye movements, no major differences in latencies were observed, which may relate to the employed experimental design, as different types of eye movements were investigated in separate blocks.

The outcomes of both experiments in the present dissertation confirm the view that saccades and vergences engaged similar cortical areas, but in varying degrees. These differences seem to reflect their specific roles in eye movement preparation and execution. Moreover, the approach used in the presented experiment, which was based on the comparison of response- and stimulus-locked activities seems to be a necessary part of analysis of different motor tasks as it allows for a more straightforward interpretation of data.

The results are crucial to better understanding how the most complicated and the least known human system – central nervous system works. Nowadays, when average lifespan significantly increases and all kinds of neural diseases from cerebrovascular accidents to neurodegenerative diseases are more and more ubiquitous, better understanding of human neurophysiology can directly influence patient's outcomes.

STRESZCZENIE

Wprowadzenie i cel badań

W celu obserwacji otaczającego nas świata, konieczne jest wykonywanie ruchów oczu, w których wyróżnić można składową sakadową i wergencyjną, czyli złożonych wergencji. Sakady są szybkimi, skokowymi ruchami oczu, które przekierowują wzrok w różnych kierunkach na jednej odległości (np. podczas czytania). Wergencje natomiast są ruchami oczu, które charakteryzują się tym, że podczas ich wykonywania oczy poruszają się w przeciwnych kierunkach. Wergencyjne ruchy oczu mogą być wyzwalane przez trzy typy wskazówek wzrokowych: dysparacje siatkówkową, rozogniskowanie obrazu na siatkówce oraz świadomość bliskości obiektu, z których dwie pierwsze są najistotniejsze. Wyróżnia się dwa rodzaje wergencji: zbieżne ruchy oczu – konwergencję oraz rozbieżne ruchy oczu – dywergencję. Chociaż złożone wergencje są ruchami oczu istotnymi dla percepcji głębi, badania nad nimi są rzadkością i tym samym kontrola neuronalna leżąca u ich podstaw jest słabo poznana. Celem niniejszej pracy było wyznaczenie obszarów kory mózgowej związanych z przygotowaniem i wykonaniem złożonych wergencji oraz określenie roli, jaką mogą one pełnić.

Niniejsza praca doktorska składa się z czterech rozdziałów: części teoretycznej, dwóch rozdziałów badawczych, które skupiają się kolejno na odruchowych i wolicjonalnych ruchach oczu oraz dyskusji końcowej. W części pierwszej skupiono się na przedstawieniu dotychczasowej wiedzy dotyczącej ruchów oczu oraz podstaw neuronalnych związanych z ich przygotowaniem i wykonaniem. W rozdziale drugim (badanie pierwsze) podjęto próbę odpowiedzi na pytanie które obszary korowe zaangażowane są w przygotowanie i wykonanie odruchowych sakad, złożonych konwergencji i złożonych dywergencji. Natomiast celem badania drugiego przedstawionego w rozdziale trzecim, było określenie obszarów korowych zaangażowanych w przygotowanie i wykonanie sakad oraz złożonych wergencji wyzwalanych wolicjonalnie (dobrowolnie).

Metoda

W badaniu pierwszym wzięło udział 16 ochotników w wieku 22.6 (SD = 0.7), natomiast w badaniu drugim 23, w wieku 23.2 (SD = 1.5). Wszyscy uczestnicy poddani

zostali badaniu optometrycznemu w celu wykluczenia zaburzeń widzenia obuocznego oraz patologii układu wzrokowego.

Ruchy oczu w obu eksperymentach wyzwalane były za pomocą układu z diodami LED. Boczna separacja diod wynosiła 10°. W eksperymencie pierwszym diody LED były umieszczone w odległości 20 cm i 100 cm od obserwatora. Każdy ruch oka rozpoczynał się pojawieniem diody centralnej umieszczonej w bliży lub w dali wzrokowej (dioda fiksacji), po którym następowało pojawienie się diody bocznej (dioda cel), wyzwalającej ruch oka. W eksperymencie drugim diody zostały umieszczone na trzech odległościach od obserwatora: 25 cm, 40 cm oraz 100 cm. W przypadku wolicjonalnych ruchów oczu, każdy typ ruchu oka (sakady, złożone konwergencje i złożone dywergencje) badany był w osobnym bloku. Ruch oka rozpoczynał się pojawieniem się diody centralnej (dioda fiksacji) umieszczonej w odległości 40 cm, która następnie zmieniała swój kolor wskazując badanemu, czy ruch oka powinien być wykonany w prawo lub w lewo, wskazując tym samym diodę cel. Zadaniem wszystkich osób badanych było jak najszybsze wykonanie ruchu oka z diody fiksacji na diodę cel.

Do pomiaru aktywności mózgu wykorzystano metodę elektoencefalografii (*ang. electoencephalography*, EEG) z wykorzystaniem 64 aktywnych elektrod (Brain Products GmBH). Zebrany sygnał EEG posłużył do wykonania analizy potencjałów wywołanych skorelowanych ze zdarzeniem (*ang. event-related potentials,* ERP), które następnie zostały opisane poprzez aktywność źródeł korowych. Do wyznaczenia korowych obszarów związanych z odruchowymi oraz wolicjonalnymi ruchami oczu wykorzystano procedurę analizy źródła elektrycznego (*ang. Brain Electrical Source Analysis,* BESA). Dzięki temu, że BESA bazuje na metodzie ERP, charakteryzującej się wysoką rozdzielczością czasową, pozwala porównać aktywność źródła wyznaczaną względem ruchu oka (*ang. response-locked activity*) z aktywnością wyznaczaną względem bodźca (*ang. stimulus-locked activity*). Przewaga aktywności wyznaczanej względem bodźca w porównaniu z aktywnością wyznaczaną względem ruchu oka sugeruje zaangażowanie danego obszaru w procesy związane z przetwarzaniem prezentowanego bodźca, podczas gdy przewaga aktywności wyznaczanej względem ruchu oka będzie wskazywać na ich zaangażowanie w procesy związane wykonaniem ruchu. Dodatkowo, w rozprawie ruchy oczu opisano za pomocą czasów reakcji, czyli latencji, które określane są poprzez interwał czasu, który upłynął od momentu pojawienia się bodźca do początku ruchu oka. Latencje wyznaczone były za pomocą elektrookulografii (ang. *electrooculography*,

EOG). Porównanie czasów latencji uzyskanych dla różnych typów ruchów oczu daje dodatkową informację na temat procesu przygotowania tych ruchów, co umożliwia precyzyjniejszą interpretację wyników, np. dłuższe latencje uzyskane dla danego typu ruchu oczu w porównaniu do innego mogą świadczyć o konieczności przetwarzania dodatkowych informacji charakterystycznych dla tych ruchów oczu.

Wyniki

Uzyskane wyniki pomiarów behawioralnych odruchowych ruchów oczu wykazały, że złożone konwergencje charakteryzują się najdłuższym czasem latencji, pośredni wynik uzyskano dla złożonych dywergencji, a najkrótszy czas latencji zarejestrowano dla sakad. Bazując na uzyskanych latencjach, analiza lokalizacji źródeł korowych została wykonana w oknie czasowym od -180 do -60 ms przed ruchem oka. Analiza głównych składowych (*ang. principal component analysis,* PCA) wykazała, że trzy źródła korowe są wystarczające do opisania 99,2% danych. Wyznaczono trzy źródła korowe, które zlokalizowane zostały w obszarze przednim czołowym (*ang. anterior frontal area*), korze potylicznej (*ang. occipital cortex*) oraz czołowym polu ocznym (*ang. frontal eye field,* FEF). Analiza statystyczna wykazała najwyższą aktywność dla kory potylicznej. Nie stwierdzono różnic w aktywności pomiędzy FEF a obszarem przednim czołowym. Z uwagi na istotne statystycznie korelacje pomiędzy aktywnością źródła zlokalizowanego w obszarze przednim czołowym a sygnałem EOG oraz umiejscowieniem tego źródła w pobliżu gałek ocznych, obserwowana aktywność w tym obszarze została uznana za artefakt wynikający z ruchu gałek ocznych. Zarówno w przypadku kory potylicznej jak i FEF, najwyższą aktywność zaobserwowano dla złożonych konwergencji, słabszą dla złożonych dywergencji, a najniższą dla sakad. Co więcej, w przypadku sakad i złożonych dywergencji zarejestrowano wyższą aktywność mierzoną względem bodźca w porównaniu do aktywności mierzonej względem ruchu oka. W przypadku złożonych konwergencji nie wykazano różnic między aktywnością mierzoną względem bodźca a aktywnością mierzoną względem ruchu oka.

Uzyskane wyniki latencji wolicjonalnych ruchów oczu wykazały, że statystycznie istotne różnice w czasach latencji dotyczą jedynie sakad i złożonych konwergencji. Uzyskane latencje posłużyły również do określenia okien czasowych, w których wykonano analizę źródła. W przypadku wolicjonalnych ruchów oczu analizę tę wykonano na ERP wyznaczonych zarówno względem ruchu oka w oknie czasowym od

-300 do -100 ms przed ruchem, jak i na ERP wyznaczonych względem pojawienia się bodźca w oknie czasowym 0 – 200 ms. Analiza głównych składowych wykazała, że dwie pary źródeł są wystarczające, aby wyjaśnić 96,9% danych aktywności mierzonej względem bodźca i 99,3% danych aktywności mierzonej względem ruchu oka.

Podobnie jak w badaniu pierwszym, zlokalizowano dwa źródła korowe związane z badanymi ruchami oczu: pierwsze w FEF, a drugie w korze potylicznej. Aktywność źródła umiejscowionego w korze potylicznej przewyższała aktywność zarejestrowaną dla FEF, zarówno w przypadku analizy wykonanej względem bodźca jak i względem ruchu oka. Wyniki uzyskane w tym badaniu wykazały przewagę aktywności mierzonej względem bodźca w porównaniu do aktywności mierzonej względem ruchu oka. Aktywność w obszarze kory potylicznej była taka sama dla wszystkich rodzajów ruchów oczu zarówno w analizie wykonanej względem bodźca jak i względem ruchu oka. W przypadku FEF zarejestrowano przewagę aktywności mierzonej względem bodźca dla złożonych wergencji w porównaniu do sakad. Co ciekawe, nie zaobserwowano różnic pomiędzy ruchami oczu w aktywności FEF wyznaczonej względem ruchu oczu.

Wnioski

Uzyskane wyniki badania nad odruchowymi ruchami oczu pokazały różnice w aktywności źródła obserwowane dla poszczególnych typów ruchów oczu w obszarze kory potylicznej (większa dla złożonych konwergencji w porównaniu do złożonych dywergencji i sakad oraz większa dla złożonych dywergencji w porównaniu do sakad). Może to wskazywać, że aktywność ta jest związana z przetwarzaniem dysparacji siatkówkowej, która jest procesem nieodłącznie związanym z wergencjami. Podobne obserwacje dotyczą FEF. Uzyskane wyniki pomiarów behawioralnych korespondują z aktywnością źródeł korowych (najdłuższe latencje obserwowane dla złożonych konwergencji, pośrednie dla złożonych dywergencji, a najkrótsze dla sakad), co dodatkowo wzmacnia hipotezę sugerującą, że różnice w aktywności wyznaczonych źródeł odzwierciedlają przetwarzanie dysparacji siatkówkowej.

W oparciu o wyniki uzyskane dla wolicjonanych ruchów oczu można stwierdzić, że w przypadku FEF, z uwagi na większą aktywność związaną ze złożonymi wergencjami w porównaniu do sakad oraz na przewagę aktywności mierzonej względem bodźca w porównaniu dla aktywności mierzonej względem ruchu, obserwowana aktywność związana mogła być z procesem przetwarzania dysparacji siatkówkowej. Natomiast brak

różnic w aktywności źródła zlokalizowanego w korze potylicznej sugeruje, że zaangażowanie tego obszaru jest niezależne od typu ruchu oka. Sugeruje to, że aktywność ta może odzwierciedlać przetwarzanie cech bodźca wyzwalającego ruch oczu lub zaangażowanie pamięci roboczej. Udział pamięci roboczej mógł wynikać z wykonywanego zadania, które wymagało zapamiętania znaczenia koloru diody LED wskazującej wymagany kierunek ruchu oczu. W przypadku wolicjonalnych ruchów oczu, wyniki czasów latencji poszczególnych typów ruchów były częściowo zgodne z wynikami uzyskanymi dla aktywności źródeł korowych (brak różnic w latencjach pomiędzy różnymi typami ruchów oczu może korespondować z brakiem różnic w aktywności źródła zlokalizowanego w korze potylicznej dla różnych rodzajów ruchów oczu).

Podsumowanie

Wyniki uzyskane w eksperymentach będących częścią niniejszej rozprawy doktorskiej potwierdzają wcześniejsze sugestie, że wergencje i sakady mogą angażować te same neuronalne korelaty, jednak w różnym stopniu. Obserwowane różnice w aktywności źródła pozwalają określić rolę, jaką pełnią one w przygotowaniu i wykonaniu ruchów oczu, a wyniki czasów latencji mogą stanowić dopełniającą wskazówkę dotyczącą interpretacji uzyskanych wyników aktywności źródeł. Co więcej, wykorzystane w przedstawionych analizach porównanie aktywności wyznaczonej względem bodźca z aktywnością wyznaczoną względem ruchu oka wydaje się być konieczne dla rzetelnej interpretacji roli jaką pełnią obszary korowe związane z ruchami oczu. Wykorzystanie tej analizy może być również pomocne w badaniu wielu innych procesów motorycznych.

Zaprezentowane wyniki poszerzają dotychczasową wiedzę dotyczącą anatomii funkcjonalnej leżącej u podstaw wergencyjnych ruchów oczu, istotnych dla postrzegania głębi. Co więcej, wyniki te mają istotne znaczenie dla lepszego zrozumienia, jak działa najbardziej skomplikowany i zarazem najmniej poznany system występujący u ludzi – ośrodkowy układ nerwowy.

1. General Introduction

1.1. Why do the eyes move?

We usually do not realize that eye movements are essential for humans' quality of vision. This crucially depends on the anatomy of our eyes, since the highest visual acuity is restricted to a 1.5 mm diameter region of the central part of the retina (i.e., the fovea), where the density of photoreceptors is the largest. Interestingly, the fovea covers only $1/4000^{th}$ of the retinal surface. Beyond the fovea, the resolution of the eye decreases with distance, being the lowest in the periphery (Fig. 1). It is worth highlighting that at two degrees from the center of the fovea, visual acuity already diminished to about 50% [1, 2]. Thus, eye movements are required to maintain the highest visual resolution.

There are two major functions of eye movements: (1) holding the image steady on the retina during head and body movements or motion of the scene, and (2) directing the fovea to new objects of interest, which are administered by the image-stabilization system and the foveation system, respectively [1, 3, 4, 5]. The image-stabilization system includes three types of eye movements providing image-stabilization strategies, since even a slight movement of the visual image on the surface of the retina (retinal slip) induces substantial blur: (1) fixation, (2) the vestibuloocular reflex (VOR), and (3) optokinetic nystagmus (OKN). Fixation holds the image of a stationary object on the fovea, the VOR holds images steady during head and body movements and is characterized by a very short latency (< 10 ms). OKN is instigated by sustained head movements or visual motion. The foveation system includes eye movements that direct the line of sight to a new object of interest: (1) saccades, (2) smooth pursuits, and (3) vergences. Saccades bring the image of an object onto the fovea, smooth pursuits hold the image of a moving target on the fovea, and vergences allow for single binocular vision by moving the eyes in opposite directions which results in the simultaneous placement of the observed object on the fovea of each eye. Nevertheless, it needs to be highlighted that in the literature some discrepancies about this division between the image-stabilization system and the foveation system can be found. The categorization of fixation to one specific system seems to be most debatable, since it is described as part of the image-stabilization system (as it was presented above), but also as part of the foveation system [5]. According to Krauzlis (2013) [6], fixation is the process observed between gaze redirections. The noticed differences in the literature may arise from the fact that fixation

is an active process, however imperceptible by the observer eye, and consists of three small eye movements: microsaccades, microdrift, and microtremor. Consequently, fixation is differently classified: active aspects of fixation fit within the foveation system, whereas holding the image on the fovea implies association with the image-stabilization system.

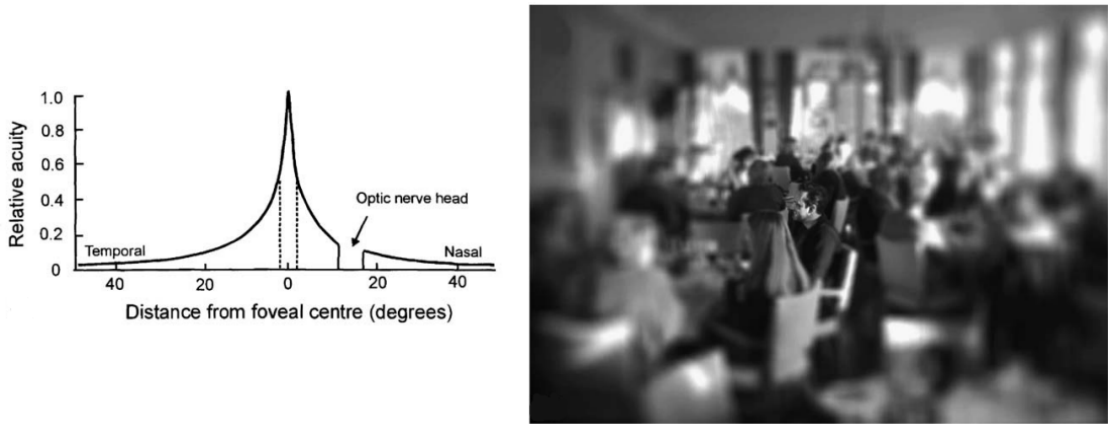

Fig. 1. The graph represents relative visual acuity across the horizontal visual field. The area between the dashed lines represents the visual acuity related to foveal vision. The picture reflects how this decrease in visual acuity affects the natural viewing condition (after *[7]*).

Eye movements may be triggered by sudden events, like the onset of a stimulus appearing in the visual periphery. They may also be triggered by intentions or goals of the observer. Based on this division, we can make a distinction between reflexive and volitional eye movements, respectively.

In this section we intended to answer the question why the eyes move. To sum up, due to the high resolution of the retina limited to central vision, eye movements enable detailed vision of the different objects which we want to see. This precise vision can be achieved for the objects of interest that initially appear in the periphery (where visual acuity is poor) and the eye movements direct the fovea to them. Moreover, eye movements provide high quality of vision also when we or the object move.

The present thesis focuses on combined vergence eye movements, in which both saccadic and vergence components can be distinguished. In the next section, saccades and vergences will be described in more detail.

1.1.1. SACCADES

Saccades are conjugate eye movements, which implies that both eyes move in the same direction. Saccades include a range of behaviors, i.e., reflexive and volitional shifts

of fixations, but also quick phases of optokinetic nystagmus and vestibular nystagmus. They also occur during rapid eye movement (REM) sleep [1]. Reflexive saccades (also referred to as visually guided saccades or prosaccades) are generated by and directed towards external, usually unexpected stimuli. A specific type of reflexive saccades is express saccades which are triggered in a gap paradigm, when observers are instructed to fixate the point which subsequently disappears (usually 200 ms) before the appearance of the novel stimulus, which elicits a saccade [8]. Among volitional saccades, different types of saccades can be distinguished: predictive saccades, memory-guided saccades, antisaccades, self-paced saccades, and endogenous (internally-guided) saccades. Predictive saccades are performed in anticipation of the appearance of a stimulus, memory-guided saccades are generated relative to a remembered location at which a target has been presented. Antisaccades, in turn, are performed in the opposite direction of a presented stimulus. Predictive saccades, memory-guided saccades and antisaccades require the engagement of additional processes characteristic for a given type of eye movement (e.g., working memory in the memory-guided task, inhibition in the antisaccade task [9], or prediction in the predictive saccades task [10]). Internally-guided saccades and self-paced saccades do not involve any specific processes being characteristic for a given type of eye movement. In the case of internally-guided saccades, a cue (usually an arrow) indicates the direction and the start of the movement, whereas during self-paced saccades the participants intentionally decide when to start an eye movement and where to move them. Nevertheless, the comparison of both types of saccades – self-paced saccades and internally-guided saccade is not straightforward, as in contrast to internally-guided saccades, self-paced saccades are not triggered by a cue [11].

1.1.2. VERGENCES

Vergence eye movements are unique among all type of eye movements, since vergences are the only disjunctive eye movements, as both eyes simultaneously move in opposite directions. Two types of vergences can be distinguished: convergences and divergences (Fig. 2). Convergences are inward eye movements, which are performed when an object of interest is closer to the observer compared to the point of fixation, or when the object moves towards the observer. Divergences are outward movements of the eyes which are performed when the object of interest is further than the point of fixation, or when the object moves away from the observer [1].

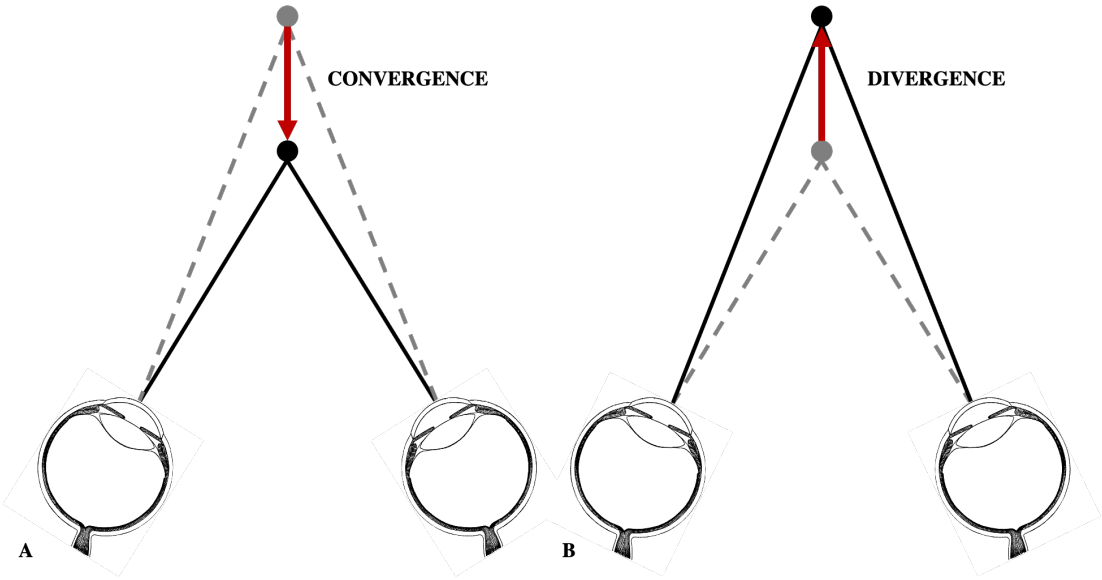

Fig. 2. Vergence eye movements. A) Convergence is an inward movement of eyes **B) Divergence** is an outward movement of eyes.

Vergences can be triggered by three types of cues: retinal blur, retinal disparity, and the awareness of the nearness of objects, however the first two are the most important cues [12]. Retinal blur is a loss of sharpness of the observed image, which triggers accommodation. It also triggers vergence eye movement and pupil constriction due to the neural connection between them. These three components work together as a near triad which is linked with neural connections between midbrain, accessory oculomotor nucleus (Edinger-Westphal nucleus – source of preganglionic parasympathetic neurons) and oculomotor nuclei [13].

A difference between the retinal images projected on the retinas in the left and right eye (i.e., retinal disparity) is the main cue that elicits vergence eye movements. The presence of disparity means that images of an object fall on non-corresponding points on the retina (i.e., the points stimulated on the retina which have different visual direction). If the size of retinal disparity prevents the fusion of both images into a single percept, double vision (diplopia) results. There are two components of disparity: the direction of disparity which indicates which objects are closer or further relative to the fixation point, and the size of disparity which provides quantitative information about how close or how far the object is [14, 15]. When fixating a distant object, presentation of a nearer object results in double vision, in a temporal (crossed) disparity with the reference to the fovea (i.e., the images of the nearer object stimulate temporal parts of retinas in left and right eye) (Fig. 3A). To see the nearer object as a single object, convergent eyes movements have to be made. When fixating the near object, the more distant previously fixated object

is imaged in a nasal (uncrossed) disparity and is seen as double (i.e., the images of the further object stimulate nasal parts of retinas in left and right eye) (Fig. 3B). To see the further object as a single, divergent eye movements are required. Moreover, the relative position of these two images of non-fixating object suggests how the angle between both eyes needs to be changed to see this object as a single and clear object. The more these two images differ, the larger convergent or divergent eye movements will be needed to perceive a single object. Since performing vergence eye movements is based on retinal disparity which is a binocular cue that provides information about depth, vergences enable perceiving objects in different depth.

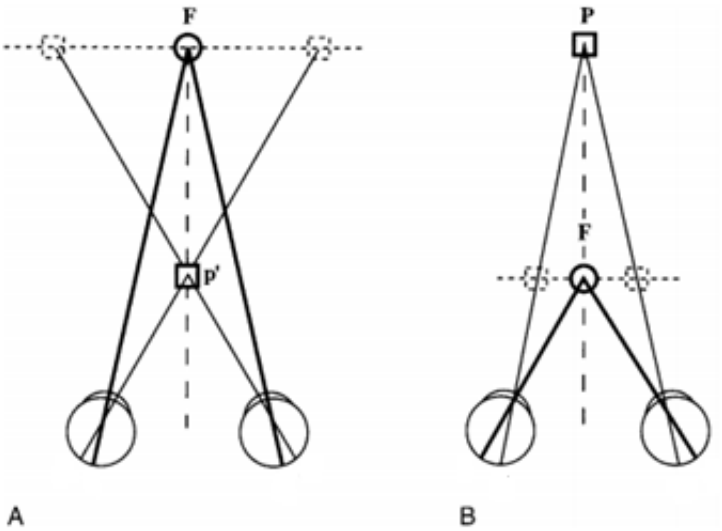

Fig. 3. Retinal disparity. A) Crossed retinal disparity - when fixating a distance object, a nearer object is seen as a double, in a temporal disparity with the reference to the fovea. To see the nearer object as a single object, convergent eyes movement have to be made. **B) Uncrossed retinal disparity** - when fixating a near object, a further object is seen as a double, in a nasal disparity with the reference to the fovea. To see the further object as a single object, divergent eyes movement has to be made (after *[16]*).

The role of vergence in the perception of distance seems evident, since vergence is perceived as one of the most important absolute distance cues, as was already hypothesized by Berkeley (1910/1709) [17]. This hypothesis was confirmed by subsequent studies by Mon-Wiliams and Tresilian (1999) [18] and Viguier et al. (2001) [19]. Moreover, Bradshaw et al. (2004) [20] suggested that vergence is considered to be an absolute distance cue necessary for reaching, which was also shown by an fMRI study of Quinlan and Culham (2007) [21]. Interestingly, a more recent study by Linton (2020) [22] revealed that the previous studies examined vergences combined with binocular retinal disparity which is another absolute distance cue. As a consequence, Linton

suggested that there is no certainty, whether vergences or retinal disparity was a crucial distance cue in these tasks. In Linton's study, binocular retinal disparity was significantly limited, i.e., the disparity that elicited vergences was so small that it was invisible for the observer. The results showed that vergences themselves were not an effective absolute distance cue, which suggests that the sensory information related to binocular disparity is more crucial for distance assessment than motor information related to vergences.

In everyday perception the different types of eye movements are intermixed as proper visual exploration requires performing multiple combined eye movements, which usually have a saccadic and a vergence component. Combined eye movements have a crucial role since they enable simultaneous gaze shifting into different depth and direction. Combined eye movements are rarely studied and largely neglected, which may be due to the complex set up needed to elicit and control them. Instead of studying the easier to control saccades, the focus of the present thesis is on combined eye movements.

1.2. THE ROLE OF ATTENTION IN THE CONTROL OF THE EYE MOVEMENTS

Attention is the function that enables the selection of relevant information from the environment, while at the same time irrelevant information is being suppressed. Reflexive and volitional attention can be distinguished (as in the case of eye movements). The former refers to attention being directed towards the events or stimuli that suddenly occur in the environment, whereas the latter refers to the attention being driven by the observer's goals [23]. It is well known that attention is strongly connected with eye movements. Groner and Groner (1989) [24] noticed that it is possible to direct attention to another place within the visual field without moving the eyes, whereas eye movement execution is probably always associated with a redirection of attention. The study by Hoffman and Subramaniam (1995) [25] revealed that accuracy of saccades was the highest when spatial attention was engaged in the task. A strong relationship between spatial attention and motor execution has been proposed according to the Premotor theory of attention, which states that spatial attention and saccade movement preparation and execution engage the same processes [26]. Interestingly, Van der Lubbe et al. (2006) [27] suggested that the relationship between spatial attention and motor preparation is not so evident as the Premotor theory of attention suggests, since they revealed that activity of parietal areas, which have been strongly associated with attentional orienting, was not

observed to be strongly related to saccade execution. Nevertheless, Van der Lubbe et al. (2006), suggested that attentional orienting may have an important role in the preparation and/or execution of actions. A recent review by Smith and Schenk (2012) [23] focused on four predictions derived from the Premotor theory of attention: (1) both motor preparation and spatial attention are controlled by the same neural correlates; (2) the goal of the movement is the same as a locus of attention; (3) motor preparation is sufficient to induce a shift of attention; (4) the oculomotor system among all effector systems has a dominant role in the orientation of spatial attention. They questioned those claims and concluded on the basis of a lot of research that motor preparation and spatial attention are not closely related. Smith and Schenk (2012) suggested that 'Premotor theory of attention should be rejected' or limited to reflexive attention which, according to their review, is the only one related to motor preparation.

1.3. WHY STUDY EYE MOVEMENTS?

Eye movements have an important role in the survival of animals that have the ability to see. They direct the fovea to object which appeared suddenly in the periphery and hold the image of this object steady on the retina which enables processing the information from the external environment. Based on this information, the decision "how to react" is made [28]. In recent years, it became clear that eye movements are related to many complex processes and have more sophisticated functions. Indeed, eye movements have become the object of interest of many different specialists varying from neurologists, psychologists, marketers, linguists, biologists. Thus, "why study eye movements?" First of all, eye movements reveal what is potentially important in the outer world, since they are quickly redirected towards those stimuli that are considered relevant for humans or animals. This observation gave rise to, for example, eye tracking studies which nowadays are widely used not only for scientific purposes but also in marketing (see: [29]). This selectivity of visual information associated with eye movements shows that eye movements may be closely linked to attentional mechanisms. People motivate this using the Premotor theory of attention, however, as indicated above, recent studies reject this relation (see: The role of attention in the control of the eye movements above).

Another motivation to study eye movements results from that neural correlates related to the eye movements are localized in almost every area of the brain. As a consequence, eye movements disorders can provide information helpful in the diagnosis

of neurological problems, for example in the case of Parkinson's disease, cerebellar ataxia, progressive supranuclear palsy, and Huntington's disease (see review: [30, 31, 32]). More recently, eye movements have been used in neuroscience to investigate cognitive and behavioral processes (for example, attention, planning, prediction) and mental disorders [28]. In the present dissertation, the focus is on vergence eye movements, which (as indicated above) are the most commonly performed type of eye movements in natural viewing conditions. Moreover, we use both eyes in the coordination controlled by vergences, which enables the fusion of two monocular images and produces binocular vision. Disorders related to vergences can be related to binocular vision problems (heterophoria or heterotropia) [33]. Therefore, the investigation of convergences and divergences and brain areas related to them, can be helpful in understanding the processes underlying binocular vision and binocular vision disorders. As these eye movements can be considered to be a window to both the brain and the mind [28], they probably will be a topic of research for many years.

1.4. BEHAVIORAL MEASURES OF EYE MOVEMENTS

Eye movements can be described by behavioral measures e.g., reaction time (RT). In general, RT and accuracy are considered to assess the efficiency and effectiveness of the task [34]. In the case of eye movements, the reaction time is often described as latency. The latency of eye movements is expressed as the time interval between the onset of a stimulus and the onset of the eye movement. Latency reflects the time necessary to determine the target position with respect to the fovea, to calculate the difference between the initial and the goal position of eyes. Subsequently, this information is converted into motor command [4].

One of the first ways to study eye movements was simply the observation of an experimenter watching participants' eye movements. Another, later method was based on the observation of afterimages induced by regularly flashing lights. Since this approach required verbal reports, it was quickly replaced by other approaches [35, 36, 37]. Lamare (1892) placed a blunt needle on the observer's upper eye lid to observe saccades which produced a sound heard by the experimenter through a rubber tube (see: [38]). The first attempts to register eye movements were made by Delabarre (1898) [39] and Huey (1898) [40] who used a lever with a pointer, which was attached to a plaster eyecup. The

movements of eye were recorded by a bristle on the smoked drum of a kymograph (the cylinder-shape device used to register and present different physiological processes).

Since the 1950s, the following methods have been developed to record eye movements which are still in use today: (1) infrared reflection devices (IRDs), (2) photoelectric methods, (3) scleral search coil, (4) electrooculography (EOG) and (5) video-oculography (VOG) (for a summary see: [37, 41]). Interestingly, nowadays web cameras of different smart devices are more often used to track eye movements [42]. As the EOG method was used to record the eye movements and to determine the latencies of eye movements in the experiments being a part of presented thesis, this technique is described in detail below.

Electrooculography is a method that registers the corneo-retinal standing potential. Due to different metabolic rates of the anterior and posterior poles of an eyeball, the charge of the cornea is about 1mV more positive than the retina, which results from the active transport of ions within retinal pigment epithelium. Therefore, the human eye acts like an electrical dipole, oriented along the visual axis. The movements of eyes result in differences in electrical potential at the skin around the eyes. For example, right eyes movement decreases the surface potential at the outer canthus of the left eye and increases the surface potential at the outer canthus of the right eye. This electrical potential can be measured using silver-silver chloride bipolar electrodes, which are usually placed bitemporally, i.e., in the outer canthus of the left and right eye. The measured potential is proportional to the sine of the angle between the visual axis and the primary eye position. It has been estimated that one degree of eye rotation results in an increase in potential of 15 – 20 μV [37]. Fig. 4 presents the measurement of the horizontal eye movements using bipolar electrodes mounted bitemporally.

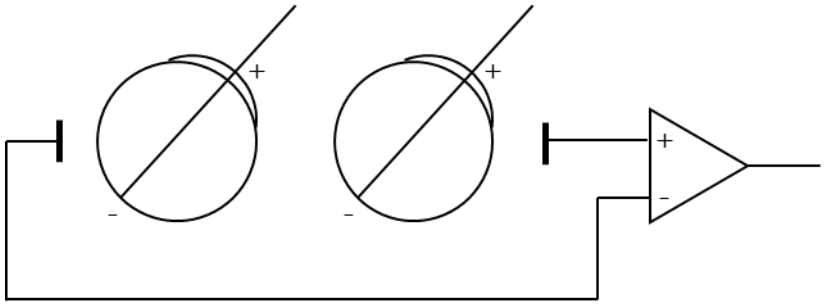

Fig. 4. The measurement of horizontal eye movements using bipolar electrodes located bitemporally.

Recently Dell'Osso et al. (2010) [35] recommended measuring each eye separately, since bitemporal placement cannot detect the disconjugancy of movements and thus does not allow to obtain correct information about eye position. Interestingly,

the International Society for Clinical Electrophysiology of Vision also recommended separate monitoring of the left and right eye in the clinical application of electrooculography [43]. In the experiments presented in this dissertation, this approach also allowed to verify what type of combined vergence actually was made. Jaschinski and Groner [33] also argued that when vergence eye movements are investigated, both eyes should be monitored separately with high accuracy. Therefore, in the experiments reported in this thesis two bipolar electrodes were used to detect horizontal eye movements which were placed on the outer and inner canthi of both the right and the left eye. To monitor vertical eye movements and blinks, another vertical position of bipolar electrodes was used (below and above the right eye). It must be remarked that vertical EOG recordings are less reliable than horizontal due to the eyelid movements and muscle artifacts [37, 41]. The electrode placement employed in the experiments presented in this thesis is presented in Fig. 5 (see: [44]).

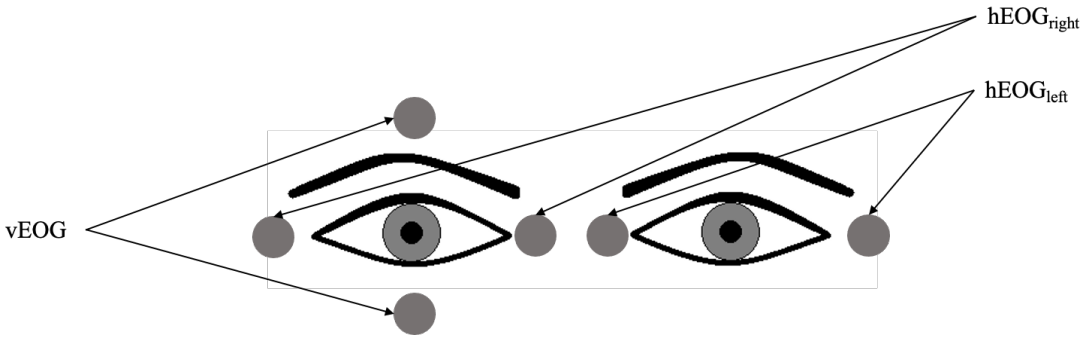

Fig. 5. Electrode placement for EOG data collection. Vertical eye movements and blinks were recorded by vertical electrodes (vEOG) located above and below the right eye, whereas horizontal eye movements were recorded by two electrodes located on the outer and inner canthi of both the right (hEOG$_{right}$) and the left (hEOG$_{left}$) eye (after *[44]*).

Although the resolution of EOG signal is limited by different types of noise that can be eliminated by applying the standards EOG recording system, an important advantage of EOG compared to other eye movement recording techniques is the possibility to record eye movements in total darkness or even with the eyes closed. Moreover, the application of EOG does not cause a lot of discomfort, as it enables wearing participants' their own glasses and does not limit the field of view [37, 41]. Moreover, a recent study by Jia and Tyler (2019) [45] revealed that the accuracy of results obtained by EOG is comparable to those recorded with video-based eye-tracking devices. They also highlighted that EOG is particularly efficient to register eye movements while measuring brain activity with electroencephalography (EEG).

Activity generated by eye movements and blinks is also an important source of noise that causes distortions in the electroencephalographic signal (particularly on frontal electrodes), which may hamper the proper interpretation of EEG data [46]. Therefore, the EOG signal is commonly used to separate the component of artifacts from the brain activity. For example, independent component analysis (ICA) can be used to remove artifacts related to eye movements from the EEG signal [47]. In our studies, which focused on the preparation of the different types of eye movements, the combined measurement of EEG with EOG was also necessary to determine the moment of making an eye movement, which made it possible to define the proper time intervals for the analyses.

1.5. ELECTROPHYSIOLOGICAL MEASURES

Over the last decades, the neurophysiology and neuroanatomy underlying eye movements became the subject of interest for many researchers (see Why study eye movements? above). Eye movements have been studied using various techniques: neuroimaging (i.e., functional magnetic resonance imaging (fMRI), positron emission tomography (PET), EEG, single-neuron recordings, lesion studies, and neural stimulation (transcranial magnetic stimulation (TMS), and transcranial direct current stimulation (tDCS)). Also, animal research provided information about the roles of brain area in eye movements. All these methods have greatly contributed to our understanding of the neurophysiology underlying eye movements and they provided complementary data. TMS and lesion studies have an important role in demonstrating causal brain-behavior relations, since the stimulation or lesion of a specific brain area may indicate if the affected brain area is necessary to perform the task. fMRI and PET, in turn, as brain imaging methods, have high spatial resolution but are characterized by limited temporal resolution. As a consequence, we cannot separately examine the processes that happen within a short amount of time. Although the EEG method has poor spatial resolution, it is characterized by high temporal resolution (up to 1 ms). This high temporal resolution enables the determination of the activity measured with a reference to different events that occur close in time, e.g., the stimulus triggering the eye movement or the actual eye movement response. Therefore, in the experiments reported in this thesis the EEG method was used, since the preparation of eye movements, i.e., the time between a go stimulus and the eye movement, lasts very shortly (about 200-300 ms depending on the type of eye

movements) and high temporal resolution is necessary to assess the differences between different types of eye movement and properly interpret the obtained data. Several aspects of the EEG method are described in detail in the following section.

1.5.1. THE NEUROPHYSIOLOGIC BASIS OF THE EEG SIGNAL

The EEG records the spontaneous electrical activity that is induced by neurons in the cerebral cortex. Neurons can generate two types of electrical activity: (1) action potentials and (2) postsynaptic potentials [48, 49]. Inside the cell of neurons high concentrations of potassium (K^+) and chloride (Cl^-) can be found, whereas outside high concentrations of sodium (Na^+) and calcium (Ca^{2+}) are maintained. This creates inside the neuron a potential difference of about -70 mV (the resting state potential) with respect to the outside of the cell membrane. Electrical or chemical stimuli modify this potential difference by opening and closing ion channels that influence the transport of ions that results in depolarization or hyperpolarization of the membrane potential [50]. The fast depolarization of the cell membrane is mediated by Na^+ ions which enter the cell. This may result in an action potential, which implies a fast depolarization followed by a return to the resting state potential. The action potential propagates down the axon. It reaches the axon terminal, where the axon forms a synapse with the following neuron and induces the release of neurotransmitters, thereby enabling the triggering of postsynaptic potentials [49, 50].

Although action potentials have larger amplitudes compared to postsynaptic potentials, they cannot be detected by surface electrodes, due to the short duration of action potentials (about single milliseconds) and the myelin insulation that is wrapped around the axon. As a consequence, action potentials in different axons do not occur with temporal overlap and also may easily cancel each other out. In turn, postsynaptic potentials, which are restricted to cell body receptors and dendrites, last ten to hundreds of milliseconds. Furthermore, both temporal and spatial summation occurs, and as a consequence, postsynaptic potentials can be easily recorded at various scalp positions [48, 50, 51]. Two types of postsynaptic potentials generated by two types of synapses (which depends on the type of neurotransmitter and receptor) can be distinguished: (1) excitatory postsynaptic potentials (EPSPs) and (2) inhibitory postsynaptic potentials (IPSPs). The EPSPs induce a flow of positive ions into cells, whereas the IPSPs induce a flow of negative ions inwards, or positive ions outwards. As a consequence, in the extracellular

space in case of ESPS a negativity is registered due to the preponderance of negative ions, whereas in case of ISPS a positivity is registered due to the preponderance of positive ions. EPSP increases the probability that the action potentials will be produced in postsynaptic neurons, whereas IPSP decreases this probability and the balance between EPSP and IPSP determines the occurring of an action potentials [49, 50, 51, 52].

The postsynaptic potentials leading to the observed EEG signal is mainly generated by pyramidal cells localized in the cortical layers III, V, and VI, which have a perpendicular orientation to the cortical surface [48, 53]. An area of positive electrical charge separated by a small distance from an area of a negative electrical charge can be described as a dipole [48, 54]. A schematic presentation of a pyramidal cell that can be characterized as a dipole is presented in Fig. 6.

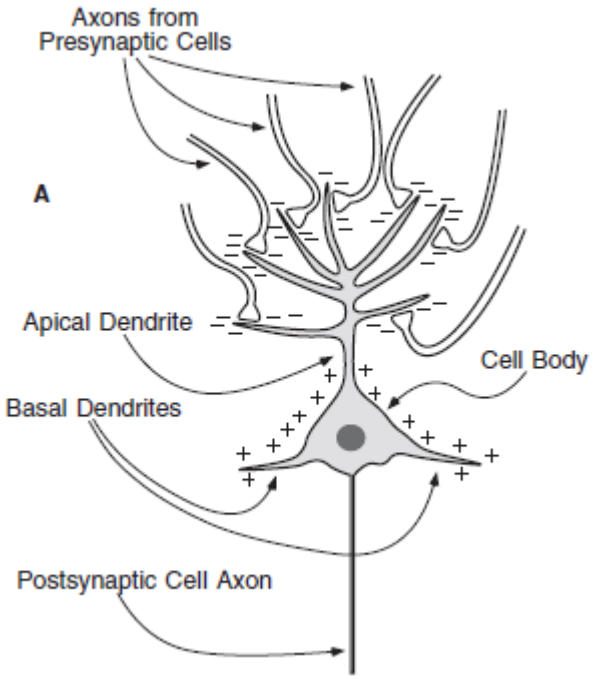

Fig. 6. The formation of dipole. The excitation of postsynaptic neurons at the apical dendrites of pyramidal cells results in negative extracellular voltage in this area compare to the area of cell body and basal dendrites. It creates a dipole, which gives rise to the EEG signal (after *[48]*).

Only these dipoles of neurons which have similar orientation and have the same input (i.e., excitatory or inhibitory) will summate the voltage at the scalp electrodes. In the case of different orientations (more than 90 degrees but less than 180) this will result in partial voltage cancellation, while complete opposite directions (180 degrees of difference in orientation) may lead to a total cancellation [48, 54].

1.5.2. THE PRINCIPLES OF EEG RECORDING

The EEG signal can be recorded at different locations over the scalp. Nowadays, most commonly used scalp electrodes are silver with silver-chloride coat (Ag/AgCl electrodes). The locations of the electrodes are often based on the extended International 10-20 system [55]. EEG systems used for scientific research may have a few (e.g., only midline electrodes) up to 256 electrodes. Moreover, dense-array sampling allows to obtain more accurate but also more complex analyses, i.e., source localization [56]. In Fig. 7 a standard electrode placement with 64 channels is shown.

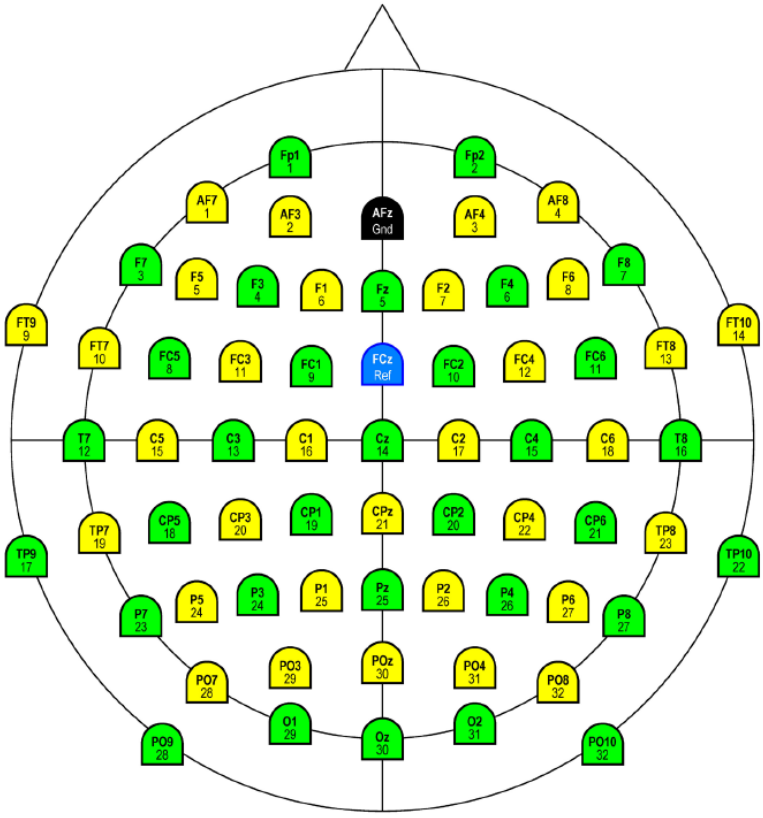

Fig. 7. Electrode montage according to the extended International 10-20 system with 64 channels, which was used in experiments being a part of presented dissertation (after Brain Products).

In the International 10-20 system nomenclature, letters describing electrode locations refer to the underlying cortical region: Fp – frontal pole, AF – anterio-frontal, F – frontal, FT – fronto-temporal, FC – fronto-central, T – temporal, C – central, TP – temporo-parietal, CP – centro-parietal, P – parietal, PO – parieto-occipital, O – occipital. The letter "z" indicates that the placement of the electrode is along the midline. Numbers, in turn, describe electrode position on the scalp with respect to the midline, where odd numbers indicate locations on the left hemisphere, while even numbers relate to locations on the right hemisphere [57]. Since the EEG signal is not a simple record of the voltage

at a single channel, but results from the differential potential between electrodes, to record the EEG signal, the use of a reference electrode (Ref) and a ground electrode (Gnd) is necessary. Thus, three types of electrodes are used to record the activity. The reference electrode allows to determine changes in brain activity registered from the scalp evoked by an experimental task by measuring a difference in electric potential between each electrode and the reference electrode. The electric potential of the reference electrode can be determined by computing an average voltage across all electrodes. Online, the reference electrode is usually placed on the subject's scalp. Use of an average reference is only possible when the electrodes are distributed along the entire head. The ground electrode is used as a common reference for all voltages in the system. It can be located somewhere on the subject's body, however it is usually placed on the forehead [48, 58]. Most EEG systems use differential amplifiers which include active, ground, and reference electrodes, i.e., they amplify the difference between the active-ground voltage and the reference-ground voltage [48, 59]. As a consequence of this subtraction, the electrical environmental noise, which would significantly affect the measured neural signal, will be eliminated.

Two types of electrodes – passive and active, can be used to obtain the EEG signal. Active electrodes, which were used in experiments being a part of the present dissertation, are thought to be superior due to the effective noise exclusion and active amplification. The study by Laszlo et al. (2014) [60] suggested that the data obtained using active electrodes was better than data obtained by passive electrodes at all impedances > 2kΩ. However, passive electrodes are better able to detect high-frequency fluctuations. The following study by Cencen et al. (2016) [61] optimized the amplification system for passive and active electrodes based on the manufacturer recommendation and concluded that the signal-to-noise ratio is comparable for both types of electrodes.

Noise present in the EEG signal can be divided into external and internal artifacts. External artifacts are usually associated with technology, e.g., mains frequency, electrode failure, or machine faults. Internal artifacts are in turn related to the actions of a participant and may come from eye movements, muscle activity, cardiac activity, skin resistance, and subject movements [62]. To obtain an artifact-free EEG signal, the reduction of skin impedance below 5 kΩ is necessary, since high impedance may create two types of problem: (1) decreased common-mode rejection, resulting from the differences in impedance between active, reference and ground electrodes and (2) increased skin potentials, which may occur when the participant moves or sweats. Common-mode

rejection is an ability of an amplifier that enables to avoid environmental noise. It depends on the impedance of the electrodes and the input impedance of the amplifier, since high impedance makes common mode rejection less effective and high input impedance allows to tolerate higher impedances of electrodes. Having low impedance before recording, which can be obtained by applying an electro-conductive gel between skin and electrode, allows to have a clean EEG signal [48, 59].

The EEG signal can be analyzed in multiple ways, for example, by performing spectral (Fourier) analyses, time-frequency (TF) analyses, or by computing event-related potentials (ERPs). The ERP method has been widely used to investigate cognitive processes, due to its high temporal resolution and the strong reduction of noise and spontaneous EEG activity. ERP analyses were employed in both experiments reported in the present dissertation (Chapter 2 and 3). The ERP method is described in the following section.

1.5.3. EVENT-RELATED POTENTIALS (ERPS)

The application of a time-locked averaging method of the EEG signal – event-related ERPs is a useful technique in assessing brain activity induced by external events or stimuli. Changes in the EEG signal may be evoked by sensory, cognitive as well as motor events. ERPs are significantly smaller than the spontaneous EEG record. The averaging of multiple trials is required to leave only summed activities of postsynaptic potentials of neurons which respond to stimulus processing or task performance. This approach enables to average out the spontaneous brain activity, and the more trials are averaged, the less spontaneous brain activities will remain. Interestingly, reducing the noise by 50% when the ERP is computed on the basis of n trials requires four times (4 * n) as many trials, as noise reduction is a function of the square root of the number of trials. It is worth mentioning here, that increasing the trials number is not the only way to decrease the noise, since it may significantly lengthen the experiment what may negatively affect participants' attention. Noise reduction can also be achieved by filtering out non-EEG signals [48]. The outcome of the averaging procedure is a voltage change over time, where the time point "zero" often relates to the appearance of a stimulus or a participant's reaction [57, 63]. However, it has been argued that the averaging procedure may result in removing (important) signals that are not strongly time-locked with the event or it may result in an inaccurate outcome, for example when two different signals

are present in different trials and the averaged waveform of ERP would contain both signals, which might suggest that both components were present on each trial (what is not true). Nevertheless, according to Luck (2005) [48], these variabilities are not problematic if you are aware of the limitation of ERP procedure and consider them in the data interpretation (the recommended rules for avoiding wrong interpretation of obtained data are described in detail in: [48]). The excellent temporal resolution of the ERP approach allows to perform: 1) stimulus-locked analyses, which reflects processes related to the processing of a stimulus; and 2) response-locked analyses, which focuses on processes related to the response of a participant. The comparison of stimulus- and response-locked activity in overlapping time intervals may enable more straightforward conclusions, since it may indicate whether the observed activity is more related to perceptual processes (when the preponderance of stimulus-locked activity is observed) or response processes (when the preponderance of response-locked activity is observed) [64]. In relation to eye movements, which were investigated in the experiments presented below, larger response-locked compared to stimulus-locked activity would suggest that this activity is related to eye movement execution, whereas larger stimulus-locked compare to response-locked activity suggests that it reflects stimulus processing. In Fig. 8, a schematic representation underlying the comparison of stimulus-locked and response-locked activity for EOG potentials is shown. The procedure of averaging both types of activity in specific time intervals is performed for the potentials registered on each or chosen electrodes.

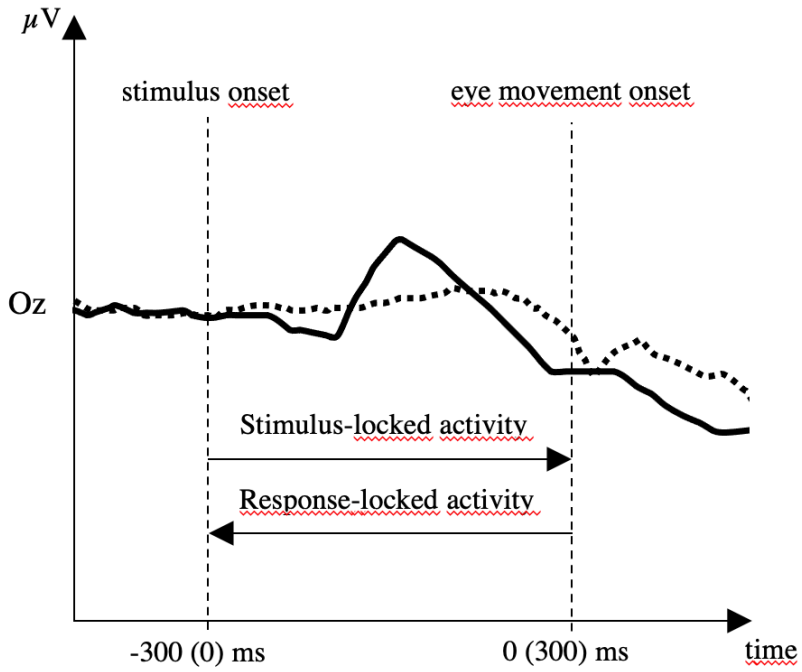

Fig. 8. The method used for the comparison of the stimulus- and response-locked activity. The procedure of determining both types of activity is performed for the potentials registered on a chosen electrode (Oz). The solid line represents stimulus-locked activity for right combined convergences, while the dashed line represents response-locked activity for these eye movements. The larger amplitude for the stimulus-locked activity suggests here that activity is more related to stimulus processing than to response execution.

1.5.3.1. VISUAL EVOKED POTENTIALS AND THEIR ORIGIN

The ERP waveform is characterized by positive and negative peaks, which are labeled by a letter (*N* – negative, *P* – positive) indicating the polarity, and number, which indicate their position within the waveform (i.e., latency). The latency is often shortened to the first number of the latency. For example, P1 means a positive component with its peak observed about 100 ms after stimulus onset. Since in the current thesis visual ERPs (also called visual evoked potentials (VEPs)) were investigated, characteristics of these components are presented below. Five components can be observed within the visual ERP waveform: C1, P1, N1, P2 and N170 [48].

The C1 component seems to be induced in the area of primary visual cortex (V1), within the calcarine sulcus, and peaks about 80 – 100 ms. Its polarity can be positive or negative, therefore it is labeled with the letter *C* [48]. The polarity of the C1 component depends on the electrode position and presentation of the stimulus relative to the

horizontal midline, since lower visual field stimulation is processing by the upper part of V1, whereas upper visual field by its lower bank [65]. Di Russo et al. (2005) [66] revealed that upper field stimuli evoked a negative component whereas lower field stimulation reversed the polarity of the peak. Due to this variable polarization the C1 is also known as N75 or P85 respectively [66, 67].

The P1 is the second component, which can be observed within the VEP waveform. This component onsets about 60 – 90 ms after the presentation of a visual stimulus, while the peak usually is in the range between 100 – 130 ms [48]. Interestingly, Di Russo et al. (2002) [68] suggested that the P1 component is characterized by an early and a late phase, observed in the 80 – 110 ms and 110 – 140 ms time windows, respectively. They suggested also that the early phase of the P1 is generated in the dorsal extrastriate cortex (the middle occipital gyrus), whereas the late phase of the P1 would be generated in the ventral occipito-temporal cortex (the posterior fusiform gyrus) [68].

The P1 component is followed by the N1 component. Di Russo et al. (2002) [68] distinguished four subcomponents of the N1 (N150, N155, N180 and N200). They appear to arise from generators that are localized within occipito-parietal, occipito-temporal, and also frontal cortex [65, 68].

Several studies showed that both the P1 and N1 components are modulated by attentional manipulations [69, 70, 71]. Van der Lubbe and Woestenburg (1997) [71] suggested that the larger amplitude of the P1 component observed on contralateral electrodes may be related to both voluntary and involuntary allocation of resources to the given location (see also: [72]).

The visual P2 component which follows the N1 component is thought to be generated in parieto-occipital regions [73] and has been related to working memory [74]. Interestingly, the dependence of the P1, N1 and P2 components on cognitive processes like attention and working memory was confirmed in a study on cognitive aging by Finnigan et al. (2011) [75]. They compared the amplitudes and latencies of P1, N1 and P2 waves in young and older adults. They observed age-related cognitive deficits in older adults investigated using word recognition task which also influenced visual ERPs, which suggests that P1, N1 and P2 components are modulated by attention and working memory.

1.5.3.2. ERP LOCALIZATION TECHNIQUES

Nowadays, probably the most challenging goal of cognitive neuroscience is to evaluate how cognitive processes are generated by specific neural circuits. To measure the activity of a specific population of neurons different techniques can be used. The most convenient methods allow to measure activity directly from the central nervous system, i.e., single-unit recording and multielectrode recording. The former technique registers the response of a single neuron, whereas the latter allows to monitor the activity from several cells at the same time. Nevertheless, both are invasive methods that are widely applied in nonhuman subject and cannot be used on human beings (except for studies on patients with implanted electrodes, suffering from neurological conditions, i.e., epilepsy or parkinsonism). fMRI, PET, and ERPs are non-invasive methods which can be applied in humans, however they all have some limitations. PET offers a spatial resolution of 2 mm, however the temporal resolution is limited by the blood flow caused by changes in neural activity, which may take up to several minutes. Similarly, fMRI, which is probably the most widely used neuroimaging technique, has a spatial resolution of 1 – 3 mm, but hemodynamic changes limit the temporal resolution to about 1 sec. Moreover, there is a complex relationship between blood oxygenation level dependent (BOLD) changes which are detected by fMRI, and neural activity, as they do not always correspond with each other. As a consequence, the interpretation of the obtained results may be difficult. Based on the low temporal resolution, one could argue that both PET and fMRI fail to investigate cognitive processes in real time. On the other hand, ERPs, in contrast to fMRI and PET, provide poor spatial resolution but has high temporal resolution [48, 76, 77].

As was indicated above, the EEG signal is an electrical potential generated by pyramidal cells that can be measured by electrodes located on the scalp (see The neurophysiologic basis of the EEG signal above). This potential is produced by electrical sources of the brain. The prediction of the EEG signal by these sources is known as the "forward problem". The "inverse problem", refers to the determination of electrical sources in the brain that are responsible for the registered potentials at the different scalp electrodes [78, 79]. The forward problem has a unique solution, since it starts from a given set of electrical sources, which generates the potentials registered by scalp electrodes, whereas the inverse problem is more complex to solve. This was already acknowledged many years ago by Helmholtz [80]. He indicated that given cortical sources indeed evokes a unique scalp topography, however many different cortical source

configurations may result in the same scalp topography. Fortunately, determination of the location of cortical activity, i.e., the inverse solution is to some extent possible, as it can be based on forward solutions. Thus, the precise determination of the forward solution is necessary to solve the inverse problem. However, one should realize that you cannot be completely sure that the estimated solution is correct [79, 81].

In recent years, researchers began to use ERP source localization methods more often to determine the likely loci of electrical sources that gave rise to the voltage distribution observed on the scalp. Solving the forward problem is quite difficult due to the inhomogeneity of the brain structures (gray and white matter surrounded by cerebrospinal fluid, the skull and scalp) and its anisotropy in the conductance (which means that conductivity is dependent on the direction, as there is for example a difference for radial and tangential conductivity). In the past, solutions assumed that the head consists of three or four spherical shells (representing mentioned earlier brain, cerebrospinal fluid, skull and scalp) and that the resistance of the head is homogenous, which significantly limited the accuracy of the models. Nowadays, different imaging techniques are used to precisely describe the shape of the head which allows to incorporate a more realistic geometry of the head (realistic models), and also to determine the resistance of the different tissue types. These solutions use numerical algorithms such as the boundary element method (BEM), the finite-element method (FEM) and the finite difference method (FDM) [48, 79, 82]. The BEM approach improves the representation of the temporal lobe as compared to spherical solutions [83], whereas FEM and FDM methods improve overall reconstruction of cortical brain areas compare to the BEM [84].

The inverse problem can be solved through forward solution using a procedure known as model fitting, which iteratively adjusts the input parameters to minimize the sum-of-square error (SSE) between data and model. In dipole source localization, measured scalp potentials distribution and model scalp potentials distribution are fitted. Following parameters are iteratively adjusted to minimize SSE: dipole location, orientation, magnitude, and time course [81]. Different methods have been developed to solve the inverse problem, which can be classified into two categories: parametric and non-parametric approaches. In the parametric approach the number of dipoles is determined a priori, which is not assumed in the non-parametric approaches. Non-parametric approaches are based on the assumption that many sources may be active simultaneously across various location at any time, therefore they are also known as the distributed source model. For a detailed review of different parametric and non-

parametric approaches see: [85]. In the experiments which are a part of a present dissertation, a parametric approach – Brain Electrical Source Analysis (BESA) was performed on the ERP data, since it allows to create more stable models compared to equivalent dipoles [86], it also enables to reconstruct the activity from one location and to separate the activity of brain areas localized in close proximity.

Estimation of the sources that best fit the obtained data may be cumbersome, due to the many possibilities of sources distribution which produce the same topography, however there are some factors which are crucial for optimizing the inverse solution. The study by Laarne et al. (2000) [87] showed that an increase in the number of electrodes which register scalp potentials improves the localization accuracy. Krings et al. (1999) [88] revealed that with 21 recording electrodes average localization error was 17 mm, whereas using 41 electrodes resulted in an average localization error of 13 mm, which confirms that employing additional electrodes on the scalp significantly improves the accuracy of source localization techniques. Moreover, each solution should have an optimal number of neural sources. Choosing the proper number of sources should be based on results from the literature but also on the employed mathematical approach (e.g., principal component analysis (PCA)). Finally, the accuracy of inverse solutions, similar to forward solution, is also dependent on head models. The question therefore arises: what is the accuracy of source localization? Interestingly, all results of the previous studies seem to be compatible and suggest that source localization is accurate to about 1 cm [88, 89].

The sources underlying the scalp potentials can be described by current dipoles or by regional sources. Current dipoles can be identified by three parameters: (1) location – which is the center of a modeled brain region of a gray matter; (2) orientation determined by orientation of the pyramidal cells, which produce postsynaptic neural currents; (3) amplitude – which reflects the postsynaptic current flow (determined in dipole moment (nAm, nanoAmpere x meter). To find the model, a set of dipoles in an initial location and orientation should be placed. Then for these dipoles the forward solution (scalp topography) is calculated, which is subsequently compared with the observed scalp distribution. The degree of mismatch is expressed as residual variance (RV), i.e., the unexplained fraction of the data variance. To reduce the RV, the adjustment of the positions and orientations of dipoles is in an iterative manner. The aim is to find a solution which sufficiently describes the data, i.e., which will be characterized by the lowest possible RV [48]. To find the most appropriate solution, methods based on, for example

Akaike information criterion, Bayesian information criterion or Wald test can also be used (see: [90]). Regional sources (RSs), in turn consist of three orthogonal vectors, which differ in length but have fixed orientation across time. For statistical analysis, the root-mean-square (RMS) can be calculated, which represents an equivalent of neural activity. RSs allow to obtain more reliable (especially in noisy data) and more stable solutions compared to equivalent dipoles, since during the fitting procedure the only location has to be determined (orientation fitting is not performed in case of RSs) [91]. The aim of the procedure of RSs fitting is the same as for equivalent dipoles fitting. The steps of the BESA approach are summarized in Fig. 9.

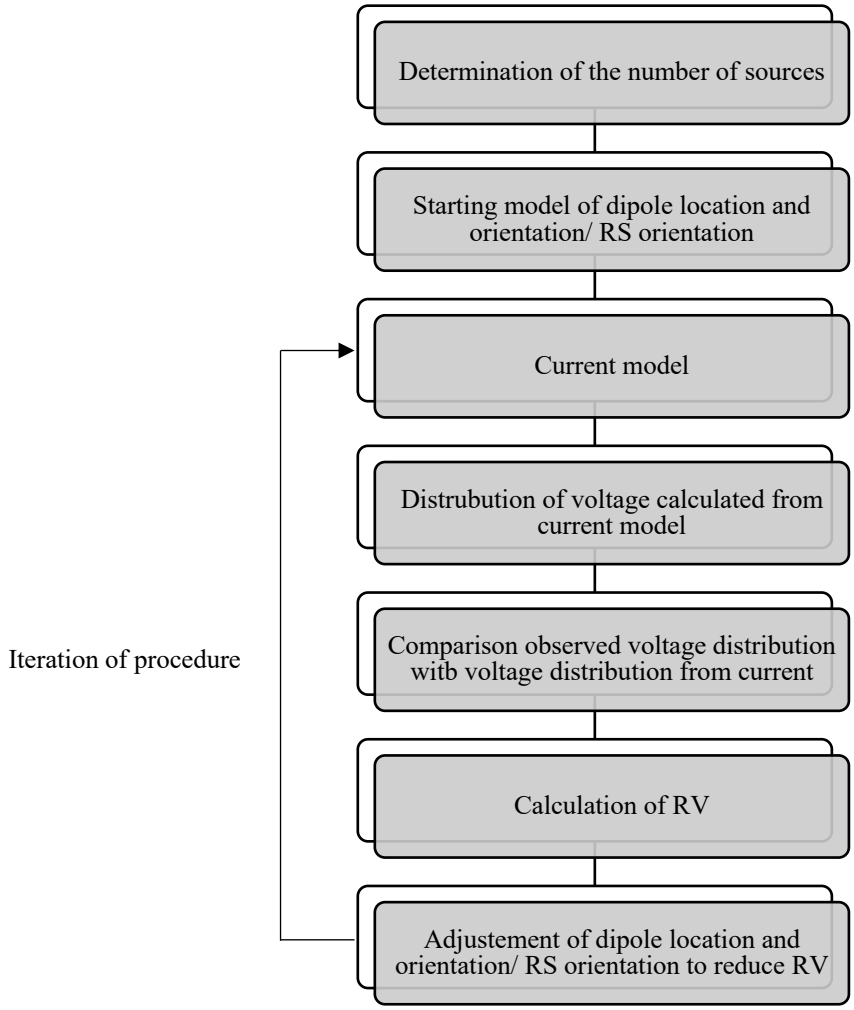

Fig. 9. The following steps of the BESA method (adapted from *[48]*).

The ERP topography related to complex cognitive processes is very often quite difficult to interpret. Although the localization of cortical sources reconstructed from ERPs seems to be convenient and useful for researchers, there are some limitations of this approach. The first problem concerns the assessment of solution accuracy, since it dependent on the noise in the data, initial assumption of the number of dipoles or RSs,

but also researchers' experience [48, 85]. However, a pilot study [92] which used a parametric approach revealed a correspondence between the brain activity observed in fMRI and the sources underlying the ERPs, despite of different temporal resolution of both approaches. A summary of forward and inverse problems is illustrated in Fig. 10.

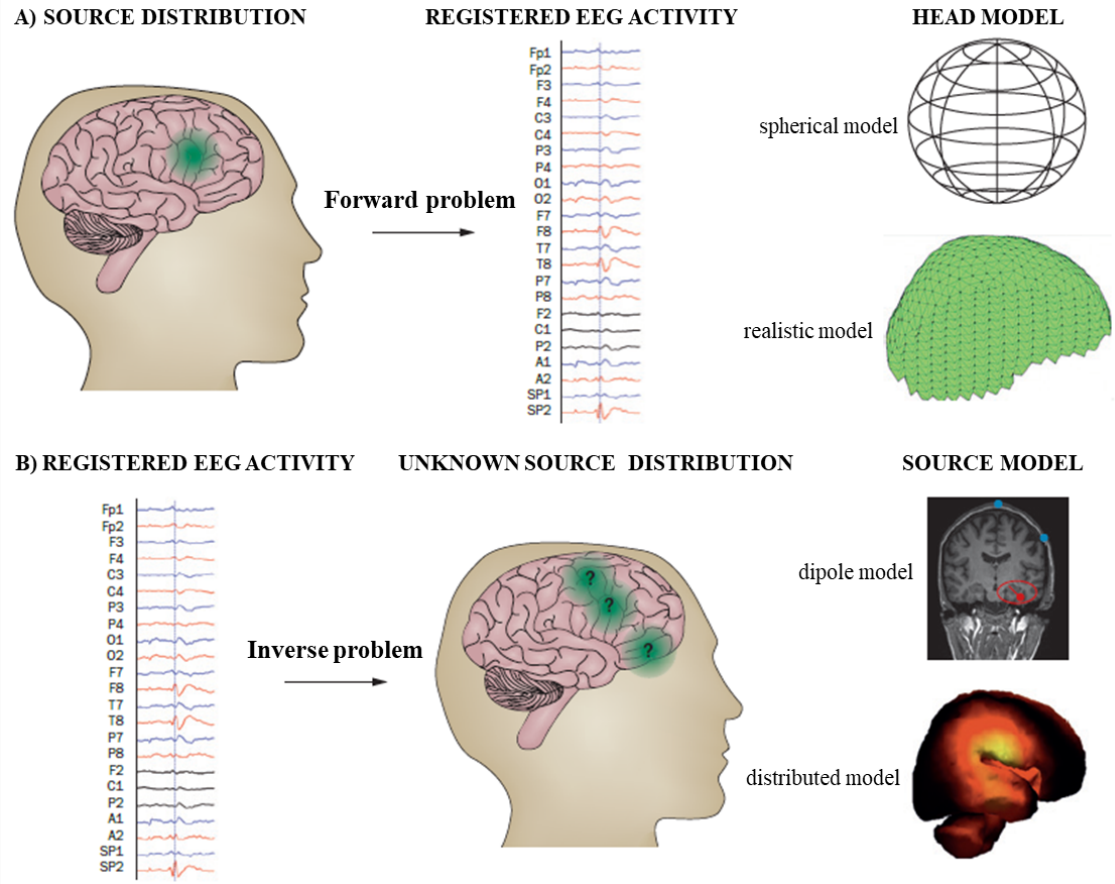

Fig. 10. A) The forward problem: the difficulty in determining EEG topography for a given source due to the anisotropy of the head. To solve the forward problem i.e., calculate the scalp potential, the head model (spherical or realistic) has to be assumed. **B) The inverse problem: an infinite number of cortical source constellations may result in the same scalp topography.** Different models can be used to solve the inverse problem i.e., determine sources underlying the scalp potential (adapted from *[93]*).

1.6. NEURAL CONTROL OF EYE MOVEMENTS

The possibility to study eye movements using various techniques provide complementary information about their neurophysiology and neuroanatomy. For example, the functional neuroimaging studies allow to observe the brain activity which reflects cognitive processes evoked by a given task, whereas lesion studies provide the information about necessity of a particular brain areas for different tasks (their preparation or execution) or cognitive processes [94, 95]. In turn, TMS changes the reaction times

and/or accuracy of a specific behavior, which indicates the causal relation between given brain areas and cognitive processes [96]. Finally, single-neuron enables direct recording of the neurons' response. In the following paragraphs, the outcomes of the studies on saccades and vergences will be described, as these types of eye movements were the subjects of our research. Moreover, as we were especially interested in the engagement of cortical areas related to eye movement preparation and execution, in the following sections, the cortical networks associated with specific types of eye movement (exogenous saccades, volitional saccades, exogenous vergences, volitional vergences) will be described.

1.6.1. CORTICAL CONTROL OF SACCADES

The first studies that focused on the neurophysiology and neuroanatomy of saccades date back from the 1960s [97]. Since that time a significant increase in the number of published papers has been observed that dealt with the determination of brain areas underlying the control of reflexive and volitional saccades and their interconnections [98]. Among different cortical areas related to saccades, we can distinguish: the primary and secondary visual cortices, dorsolateral prefrontal cortex (DLPFC) and three types of eye fields: the parietal eye fields (PEF), which are a part of the posterior parietal cortex (PPC), the frontal eye fields (FEF), and the supplementary eye fields (SEF). In the following paragraphs detailed description of the presumed roles of these areas in the preparation and/or execution of both reflexive and volitional saccades will be presented.

1.6.1.1. CORTICAL CONTROL OF REFLEXIVE SACCADES

It is well known that the superior colliculus (SC) has an important role in the triggering of fast eye movements like prosaccades (the role of SC in eye movement generation is described in detail below). Nevertheless, Experiment 1 in the current dissertation (Chapter 3) revealed that cortical areas have an important role in the preparation of reflexive saccades. Therefore, the following section aims at summarizing the previous knowledge about cortical areas related to preparation and execution of reflexive saccades.

Previous studies revealed that the occipital cortex, parietal cortex and an area within the frontal cortex – the FEF are strongly associated with the preparation and

execution of exogenous saccades. The involvement of visual cortices in reflexive saccades is not surprising, since reflexive saccades are guided by visual information, i.e., visual stimuli which suddenly appear in the periphery of the visual field. Therefore, the activity within visual cortex may be related to the processing of features of stimuli, which evoke the eye movements [99, 100, 101, 102] or may be associated with the primary role of these areas in the projection to higher-order cortical areas [99, 100]. Taken together, it seems that the occipital cortex provides visual information during motor planning to those brain areas which are related to the motor execution [103]. The studies by Tehovnik et al. (2004, 2005) [104, 105] revealed that microstimulation of macaque V1 resulted in a delay in visually-guided saccades, which underlines the role of this area in exogenous saccades, which may mean that V1 has a role in the disengagement of fixation.

As mentioned before, the occipital cortex is rather related to the processing of visual information triggering saccades, whereas three types of eye fields are strongly related to the various aspects of reflexive saccades preparation and execution. Heide and Kömpf (1998) [106] and Gaymard et al. (2003) [107] suggested that the PEF is a crucial structure in the process of disengaging fixation and thus triggering exogenous saccades, since they revealed that lesion of parietal areas caused saccade inaccuracy and delay. These findings are in line with TMS studies which revealed that microstimulation of PPC (which includes PEF) also increased the latency of reflexive saccade [108, 109]. Interestingly, Pierrot-Deseilligny et al. (1991) [110] revealed in their lesion study that the engagement of parietal areas in exogenous saccades task may differ between the right and left hemisphere. They showed that the right PPC has a crucial role in the control of exogenous saccades, since lesion of the right PPC resulted in increased latencies of horizontal right and left saccades, whereas lesion of the left PPC affected only right saccades. A recent study by Diana et al. (2021) [111] also emphasized the role of the right PPC in exogenous saccades, since they revealed that anodal tDCS over right PPC resulted in shorter latencies for right and left exogenous saccades.

Interestingly, these observations may be related to attention, since Heilman and Van Den Abell [112] formulated a theory (subsequently confirmed by Mesulam [113]) that the right hemisphere is involved in directing attention to the left and right visual fields, whereas the left hemisphere is only involved in directing attention to the right external space. In general, right parietal cortex is thought to be highly associated with spatial attention [114, 115]. Corbetta et al. (1998) [116] and Perry and Zeki (2000) [117] observed an increase in the activity of PEF for reflexive saccades, but also for shifting

attention to a given direction without gaze shifting. Based on these studies, it may be concluded that it is difficult to differentiate whether the observed activity in PEF reflects a process related to eye movement preparation and execution or processes associated with the orienting of attention. Based on these overlapping cortical networks, there was a hypothesis which suggests that attentional and oculomotor processes are highly integrated [118], which seem to be in line with the modified Premotor theory of attention that suggests that it should be limited only to exogenous attention (see The role of attention in the control of the eye movements above).

There is also an area within the frontal lobe - FEF, which can be associated with reflexive saccades, however, its role in this type of eye movements is not very clear. Schiller and Tehovnik (2005) [119] revealed that lesion of the FEF in macaques interfered with target selection, whereas Segraves and Park (1993) [120] showed that lesion of the FEF affected the accuracy of reflexive saccades. Human studies, in turn, suggested that FEF lesions only slightly impaired the latencies of reflexive saccades [110, 121]. All these mentioned studies showed that FEF may indeed control exogenous saccades, however it is generally emphasized that FEF is more engaged in volitional saccades preparation and generation [9, 122, 123, 124]. However, a recent study by Diana et al. (2021) [111] showed that tDCS over the right FEF reduced the onset latencies of saccades. Nevertheless, it should be noted that tDCS studies over FEF are inconclusive, since a study by Reteig et al. (2018) [125] revealed that neither cathodal nor anodal stimulation affected accuracy or latencies of prosaccades. An explanation of these differences may be motivated by a recent study of Dash et al. (2020) [126], as they revealed that inactivation of FEF in rhesus monkeys resulted in the impaired ability to perform express saccades, but this manipulation did not completely inhibit them. Based on these outcomes, it may be concluded that the FEF is not a crucial structure for the generation of express saccades [126].

The SEF and DLPFC seem to be strongly related to volitional control of saccades [127, 128, 129, 130]. For example, in the study by Furlan et al. (2016) [130] a response in cortical and subcortical areas related to the preparation of anti-saccades and prosaccades was compared using fMRI. Findings revealed that for cortical areas (i.e., FEF, DLPFC and IPS) activity related to antisaccades was significantly larger than those related to prosaccades. A detailed description of cortical circuities related to the volitionally triggered saccadic eye movements is presented in the next section.

1.6.1.2. CORTICAL CONTROL OF VOLITIONAL SACCADES

The neural circuity associated with volitional saccades has been determined with memory-guided saccades, antisaccades, self-paced saccades, and endogenous saccades (for a description of these eye movements see Saccades above). In the case of volitional eye movements various areas are activated to perform accurate eye movements. Beyond occipital cortex of which the engagement is not crucial for volitional saccades, there are three areas located within frontal lobe that are thought to be strongly involved in the intentional exploration of the environment: FEF, SEF and DLPFC.

The engagement of occipital areas reflects probably the processes related to the stimuli which trigger eye movements as in the case of reflexive saccades. Interestingly, previous studies suggested that the activity within visual cortex for volitional saccades, i.e., antisaccades is generally lower than for exogenous saccades (see: [98]). For example, in the EEG/MEG study by McDowell et al. (2005) [131] post-stimulus activity in the middle occipital gyrus was larger for prosaccades compared to antisaccades. This difference can be explained by the top-down processes engaged in antisaccade task from higher-level cortices which attenuates activity within visual cortex.

Higher-order cortical areas (FEF, SEF and DLPFC) are involved with more specific tasks associated with the preparation and execution of volitional saccades. In contrast to the occipital cortex which reveals larger activity for exogenous saccades, these areas are considered to be more active in case of volitional saccades [131]. Previous fMRI studies showed stronger activation of the FEF before antisaccades compared to exogenous saccades [130, 132, 133, 134, 135]. Interestingly, the TMS study by Yang and Kapoula (2011) [136] showed that the FEF control memory-guided saccades, since TMS stimulation over FEF affected this type of eye movements. Cameron et al. (2015) [137] suggested that the engagement of the FEF reflects the processes related to the preparation of eye movements rather than movement execution.

Although the engagement of the FEF in the antisaccade task seems clear and is probably related to the triggering of the antisaccade [138], activation of other cortical areas – SEF and DLPFC is also necessary to correctly perform antisaccades [124]. Increased activity within SEF observed before antisaccades allows to control the tendency to look at the peripheral stimulus and thereby allows to perform antisaccades instead of performing prosaccades [133, 139]. Therefore, it seems that SEF may be an important region that inhibits reflexive eye movements toward stimulus. Amador et al. (2004) [140]

in the study on macaques also emphasized the engagement of the SEF in the antisaccade task, since they revealed that neurons in SEF fired more prior to antisaccades compared to prosaccades. Apart from being involved in antisaccades, the SEF are also engaged in tasks requiring the execution of a sequence of saccades [141, 142].

DLPFC seems to have a crucial role in overall cognitive control, i.e., attention, planning, spatial orientation etc. [143]. As mentioned before, the role of DLPFC in antisaccades seems to be crucial. EEG/MEG and fMRI studies found larger activity within DLPFC also for antisaccades compared to prosaccades [131, 144] and studies on patient with lesion of DLPFC demonstrated increased percentage of errors while performing antisaccades [129, 145]. A possible explanation of these results is that in the case of antisaccades activation of DLPFC may reflect inhibition of reflexive saccades [146]. Pierrot-Deseilligny et al. (2003) [145] based on the lesion studies revealed the role of DLPFC also in memory-guided saccades. As the amplitude of memory-guided saccades is thought to reflect spatial memory processes, DLPFC is considered to be an important structure controlling this cognitive process, which was also confirmed by TMS [147] and fMRI [148] studies. Finally, the study by Pierrot-Deseilligny (2003) [145] showed that lesion of DLPFC have resulted in decrease in the percentage of saccades in predictive task what suggests that DLPFC also controls predictive saccades [129].

A simplified scheme showing cortical (and subcortical) areas engaged in the control of saccades is presented in Fig. 11. Furthermore, a summary of the roles which cortical areas have in the preparation and/or execution of reflexive and volitional saccades is presented in Table 1. The SC is the most important structure on the subcortical level that controls saccades execution. According to Neggers et al. (2005) [149] and McPeek and Keller (2004) [150] SC controls the fixation and the generation of saccades. As PEF and FEF independently control reflexive and volitional saccades respectively, they both have independent connections to the SC [118]. Moreover, previous studies suggested the presence of reciprocal connections between FEF and PEF, which are related to processing the information associated with sensory aspects of spatial attention [151]. Although the engagement of FEF in reflexive saccades and PEF in volitional saccades is not clear, Gaymard et al. (1998) [152] suggested that the predictability of visual targets may engage the FEF and in that case the direct parieto-tectal pathway (from PEF do SC) is no longer engaged. In turn, in the case of volitional saccades, the engagement of PEF may reflect integration of visual information in a spatial map, which is subsequently stored in DLPFC (in case of memory-guided saccades). Therefore, DLPFC may provide signals that

activate neurons within FEF [137]. Interestingly, the inhibition of reflexive saccades in the antisaccade task controlled by DLPFC probably reaches the SC by an independent connection [153]. The SEF, like the DLPFC also projects to FEF [127]. Taken together, it may be concluded that several cortical areas are engaged in high-level control of saccades related to specific tasks, whereas SC has a crucial role in the eye movement execution [130].

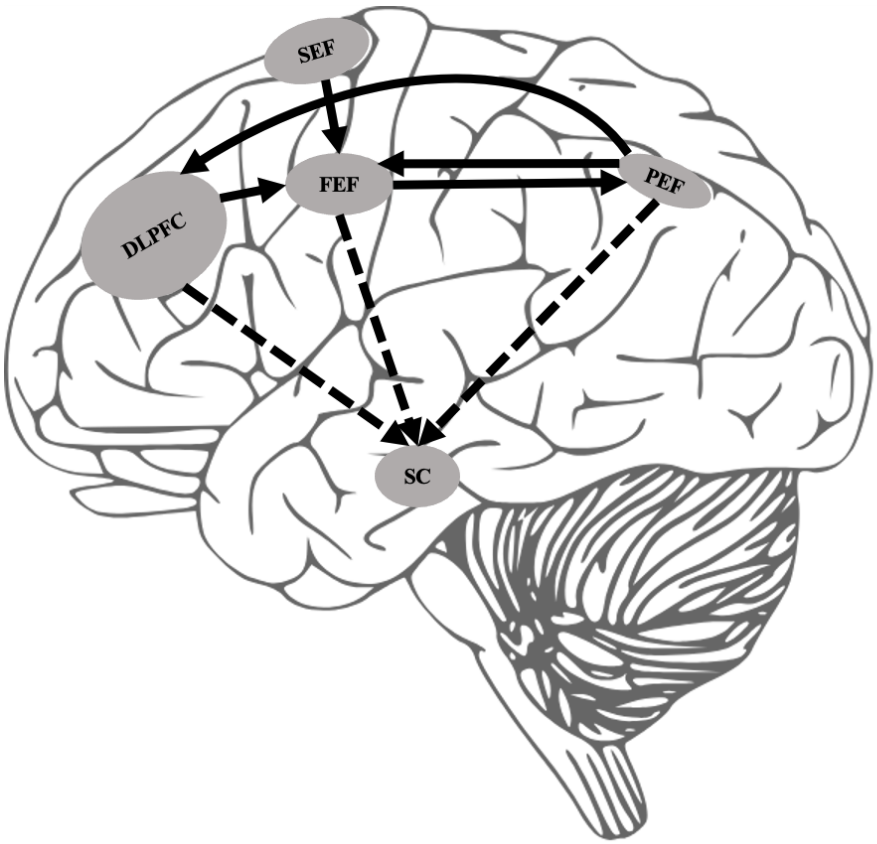

Fig. 11. A simplified scheme presenting main cortical and subcortical areas engaged in control of reflexive and volitional saccades (DLPFC – dorsolateral prefrontal cortex; FEF – frontal eye field; PEF – parietal eye field; SEF – supplementary eye field; SC – superior colliculus). Solid lines represent cortico-cortical connections between the brain structures, whereas dashed lines represent cortico-subcortical connections (based on: *[118, 124, 129]*.

Table 1. Summary of the roles of different cortical brain areas in the preparation and/or execution of reflexive and volitional saccades (DLPFC – dorsolateral prefrontal cortex; FEF – frontal eye field; SEF – supplementary eye field).

Cortical area	Role
FEF	Preparation of different types of volitional saccades
DLPFC	Inhibition of reflexive saccades in antisaccade task Short-term spatial memory in memory guided saccades Prediction in predictive saccade task
SEF	Inhibition of reflexive saccades in antisaccade task Control sequences of saccades
Parietal cortex	Fixation disengagement in reflexive saccades Spatial attention

1.6.2. CORTICAL CONTROL OF VERGENCES

In everyday life we explore the environment not only through directing the gaze in different directions performing saccades, but also in different depths by performing vergences. Vergences engage the same cortical areas as saccades, but in different degrees [154]. This differential involvement that depends on the type of eye movements may be related to attentional and/or visuomotoric processes associated with the cue that trigger vergences – binocular retinal disparity. Fig. 12 explains the differences in visumotoric processes between saccades and vergences. In the case of saccades (Fig. 12A) the images of the target (red circle) and stimuli which can elicit saccades (green and blue circles) fall on corresponding retinal points of left and right eyes. Corresponding retinal points are the points that have the same visual directions, i.e., points on the temporal retina of one eye corresponds with the points on the nasal retina of the other eye and vice versa. Foveas are also corresponding points. Since red, blue and green circles in Fig. 12A stimulate corresponding points of the retinas, they are fused and perceived as single points. In the case of vergences (Fig. 12B) non-corresponding points are stimulated, i.e., when the red circle is observed, the images of the stimulus which is further from the observer (blue circle) stimulates nasal parts of the retina in both eyes and triggers divergence. In turn, a stimulus that is closer to the observer (green circle) stimulates temporal parts of the retina in both eyes and triggers convergence.

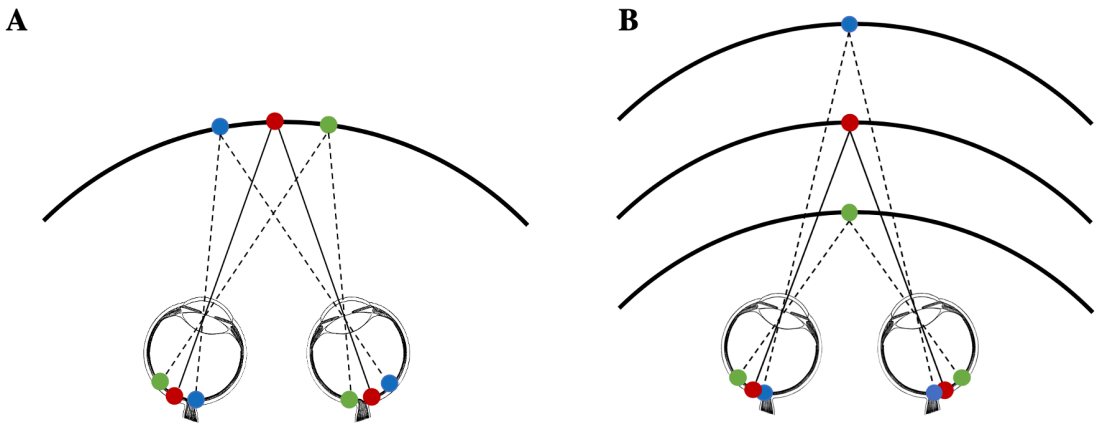

Fig. 12. The differences in visuomotoric processes related to saccades (A) and vergences (B). Saccades are triggered by the retinal images of the stimuli which falls on the corresponding retinal points, i.e., stimulates nasal parts of one eye and temporal parts of another eye, whereas vergences are triggered by the retinal images of the stimuli which falls on the non-corresponding retinal points, i.e., stimulates nasal or temporal parts of both eyes.

The first observations related to the cortical and subcortical control of vergences came from studies that did not investigate vergence eye movements per se but focused on retinal disparities triggered by stereoscopic images. For example, disparity-tuned cells have been found in macaques' V1, V2 and V3 visual cortices [155, 156, 157] and in V1, V2 and SC of a cats' brain [158, 159].

1.6.2.1. CORTICAL CONTROL OF REFLEXIVE VERGENCES

Reflexive vergences in humans were investigated using TMS, EEG, and fMRI. One of the first studies used TMS [108]. Kapoula et al. (2001) [108] revealed that stimulation of PPC not only increased the latency of reflexive saccades (see Cortical control of reflexive saccades above) but also reflexive vergences, which suggests that parietal cortex is crucial for different types of reflexive eye movements.

Crucial findings related to reflexive vergences were reported in two first EEG studies in humans [160, 161]. In the study by Kapoula et al. (2002) [160] pure divergences were related to larger ERPs (more negative) compared to pure convergences. Similar findings concerned combined eye movement, i.e., more negativity preceding combined divergences compared to combined convergences. Although determination of the topography related to the vergences was not possible in this study, due to the limited number of participants and electrodes, Kapoula et al. (2002) suggested that frontal and parietal areas are engaged in vergence preparation. Second EEG study by Tzelepi et al.

(2004) [161] showed in turn that convergences were preceded by more negativity than divergences with highest amplitudes above posterior and central areas. The negativity for divergences was distributed along the ventral pathway. Although both studies focused on saccades, pure vergences and combined vergences, they employed different approaches to analyze the data, i.e., Kapoula et al. (2002) investigated response-locked activity, whereas Tzelepi et al. (2004) investigated stimulus-locked activity (see paragraph Event-related potentials above), which may explain the differences observed in both studies. However, these differences may be explained also by variations in the experimental design, since in the study by Tzelepi et al. (2004) divergences were more predictable than convergences, which could have decreased the cortical activity related to predictable targets. Therefore, Przekoracka-Krawczyk et al. (2018) [162] tried to determine whether convergence or divergence induce a higher and wider cortical activity using the paradigm which did not allow to predict the following eye movements. They also adjusted the brightness of the stimuli (LEDs) placed at different depth. Thus, any difference observed in the ERPs were related to the eye movements. They observed higher cortical activity related to convergences, so the findings reported by Tzelepi et al. (2004) do not appear to be the result of anticipation. Hence, the differences between the studies by Kapoula et al. (2002) and Tzelepi et al (2004) may result from the employed type of analysis. Nevertheless, the best way to confirm this hypothesis is to perform both types of analysis, i.e., stimulus-locked and response-locked analyses using the same data, as was done in the present dissertation (see Chapter 2 and 3).

According to our knowledge, there is also one fMRI study that investigated reflexive saccades and vergences in which they compared neural correlates underlying both reflexive saccades and vergences [154]. Interestingly, Alkan et al. (2011) [154] revealed that both types of eye movements involve similar cortical regions: SEF, DLPFC and posterior cingulate cortex (PCC). Only activity within the FEF showed a spatial difference, since vergences activated a region that was shifted more anteriorly as compared to saccades. Alkan et al. (2011) suggested that the roles of these areas in vergences are similar to these which they have in case of preparation and execution saccades (see Table 1 above). Alkan et al. (2011) suggested also that areas that may reveal association with vergences are the FEF and the parietal regions. Previous studies on eye movements, but also on hand reaching in depth suggested that disparity is encoded within parietal lobe [21, 163, 164, 165]. The neurons sensitive to disparity were also found in FEF [166, 167].

1.6.2.2. CORTICAL CONTROL OF VOLITIONAL VERGENCES

Volitional vergences are probably the least-examined type of eye movements in terms of their cortical and subcortical control. The neural control related to the volitional vergences was initially investigated on primates by Gamlin and Yoon (2000) [167]. The idea that cortical regions may have an important role in vergence eye movements comes from the observation of anatomical connections existing between cortical and subcortical areas as it is in case of FEF, which has connections with subcortical areas sensitive to disparity. It was a motivation for Gamlin and Yoon (2000) to formulate the hypothesis that the FEF may be related with vergences. Indeed, they found that an area of the frontal cortex which is located nearby to the saccade-related FEF is strongly associated with vergences (and accommodation as well). Moreover, they also suggested that this activity is related to the motoric aspect of vergences rather than sensory aspects, i.e., retinal disparity of the presented target. The sensitiveness of FEF neurons to retinal disparity was also shown by another study on monkeys by Ferraina et al. (2000) [166], which supports the role of FEF in vergence eye movements.

According to our knowledge, there is only one study that investigated volitional vergence eye movements in humans [168]. In this study, Alverez et al. (2010) [168] compared cortical correlates underlying predictive vergences and saccades using fMRI. In such a task, the participant anticipates the next target, since following stimuli occur in a repeatable order. The results revealed that both saccades and vergences involved similar cortical regions: FEF, SEF, DLPFC, PEF. Interestingly, Alvarez et al. (2010) observed only one difference between predictive saccades and vergences which strongly correlates with the observation made by Gamlin and Yoon (2000), i.e., vergence-related SEF and FEF are located more anteriorly compared to saccade-related SEF and FEF.

Finally, there is one study that previously compared reflexive and predictive vergences and saccades [169]. As the previous studies noted that saccades and vergences involve similar neural circuities, Alkan et al. (2011) used fMRI to investigate how these regions interact with each other. Interestingly, they revealed that when predictive eye movements were performed, more connections (i.e., number of directed influences) between brain areas were observed compared to reflexive eye movements. More connections were also registered during vergences compare to saccades.

1.7. QUESTIONS TO BE ADDRESSED IN THE PRESENT DISSERTATION

Although it seems that vergence and saccades involve similar cortical regions, the specific roles that these areas have in vergence eye movements (especially exogenous, which do not engage additional complex cognitive processes) is not clear. The application of the EEG technique which is characterized by high temporal resolution allows to determine the temporal dynamics of the involved cortical mechanisms underlying vergence eye movements and also allows to compare the activity related to stimulus processing and motoric preparation and execution. The comparison of stimulus- and response-locked activities will enable specifying the roles of engaged cortical areas, since the preponderance of stimulus-locked activity suggests the involvement of the area in target processing, whereas preponderance of response-locked activity will reflect engagement in eye movement execution.

In the following two empirical chapters, the influence of preparation and execution of saccades and vergences on cortical activity will be described. The following questions will be addressed:

Which cortical areas are related to the execution and preparation of exogenous saccades and combined vergences and what are their respective roles?

In Chapter 2, cortical activity measured by EEG underlying exogenous saccades, combined convergences and combined divergences will be extensively described. As a comparison of ERP topographies may not lead to clear conclusions, due to the low spatial resolution of ERPs, observed ERPs will be describe by different cortical sources with different activity patterns over time using the BESA method. The pattern of activities observed for saccades, combined convergences and combined divergences will be compared and also stimulus- and response-locked activities to more precisely conclude about the roles of the cortical areas related to eye movements.

Which cortical areas are crucial for the execution and preparation of endogenous saccades, combined vergences and what are their respective roles?

In Chapter 3, electrophysiological results related to endogenous saccades, combined convergences and combined divergences will be presented. As we would like to compare these results with findings with exogenous eye movements from the Chapter 2, the BESA

technique was also used. We would like to determine relevant areas for endogenous eye movements and also specify their roles based on comparison of stimulus- and response-locked activities. According to our knowledge, this is the first study using a source analysis on ERPs to specify the cortical areas related to the execution of endogenous saccades, combined divergences and convergences.

Do exogenous and endogenous eye movements indeed engage the same cortical structures? Is there any difference in a pattern of activities for combined vergences and saccades?

As designs of both presented experiments were very similar in the terms of types of investigated eye movements and used stimuli (i.e., use one stimulus indicated both the direction and the moment of the required eye movement in both experiments), in the summary of a present dissertation extensive discussion related to the differences in cortical activity between the different types of eye movements will be presented.

2. THE ENGAGEMENT OF CORTICAL AREAS PRECEDING EXOGENOUS VERGENCE EYE MOVEMENTS[1]

This chapter is based on the published paper:
Wojtczak-Kwaśniewska M, Przekoracka-Krawczyk A, Van der Lubbe RHJ (2018) The engagement of cortical areas preceding exogenous vergence eye movements. PLoS ONE 13(6): e0198405. https://doi.org/10.1371/journal.pone.0198405

In the following version of the article, the numbering of the references and figures has changed compared to the version published in the PLOS One in order to maintain the continuity of both lists within the dissertation.

[1] The authors confirm their contribution to this paper as follows: 70% Monika Wojtczak-Kwaśniewska, 15% Anna Przekoracka-Krawczyk, 15% Rob van der Lubbe. Detailed contributions are described in the Author contribution statements in Appendix 1, Appendix 2 and Appendix 3, attached at the end of the dissertation.

Abstract

Source analyses on event related potentials (ERPs) derived from the electroencephalogram (EEG) were performed to examine the respective roles of cortical areas preceding exogenously triggered saccades, combined convergences, and combined divergences. All eye movements were triggered by the offset of a central fixation light emitting diode (LED) and the onset of a lateral LED at various depths in an otherwise fully darkened room. Our analyses revealed that three source pairs, two located in the frontal lobe: the frontal eye fields (FEF) and an anterior frontal area, and one located within the occipital cortex, can account for 99.2 % of the observed ERPs. Overall, the comparison between source activities revealed the largest activity in the occipital cortex, while no difference in activity between FEF and the anterior frontal area was obtained. For all sources, increased activity was observed for combined vergences, especially combined convergences, relative to saccades. Behavioral results revealed that onset latencies were longest for combined convergences, intermediate for combined divergences, and the shortest for saccades. Together, these findings fit within a perspective in which both occipital and frontal areas play an important role in retinal disparity detection. In the case of saccades and combined divergences stimulus-locked activity was larger than response-locked activity, while no difference between stimulus- and response-locked activity was observed for combined convergences. These findings seem to imply that the electrophysiological activity preceding exogenous eye movements consists of a sensory-related part that is under cortical control, while subcortical structures may be held responsible for final execution.

2.1. INTRODUCTION

Eye movements play an integral and crucial role in human vision, as for the detailed perception of objects their respective images have to be properly projected on the fovea. Three types of eye movements are responsible for adjusting our gaze and directing the line of sight to a new object of interest: smooth pursuit, saccades, and vergences [1, 3]. While smooth pursuits hold the image of a moving target on the fovea and saccades bring images of the target onto the fovea, vergences move the eyes in opposite directions to project the images of an object on the fovea of both eyes simultaneously [1]. Pure saccades and pure vergences are rarely observed as separate eye movements in everyday life, since exploring the environment mostly consists of a combination of these eye movements. Although the neural circuitry relevant for pure eye movements, mainly saccades, has been widely explored, the neuroanatomy of combined eye movements is not well understood. In the current study, we intend to demonstrate that reflexive (i.e., exogenous) combined eye movements may involve similar cortical areas as saccades. However, different types of eye movements may involve different cortical areas in varying degrees. Source analyses on event related potentials (ERPs) preceding eye movements, which can be derived from the electroencephalogram (EEG), were carried out to determine the likely involvement of different cortical areas over time.

The functional anatomy underlying the execution of saccades, both reflexive, visually guided (exogenous), and volitional (endogenous) saccades in humans, is well known. Saccades have been extensively studied using various methods, including functional neuroimaging studies (i.e., functional magnetic resonance imaging (fMRI), positron emission tomography (PET), electroencephalography (EEG)), neural stimulation (i.e. transcranial magnetic stimulation (TMS)), lesion studies, and single-neuron recordings. All these methods have greatly contributed to our understanding of the neurophysiology and neuroanatomy of saccades, since they provided complementary data (for reviews see: [98, 138, 152, 153, 170, 171, 172]).

The global view that emerged from the aforementioned studies is the engagement of several subcortical and cortical regions while executing reflexive saccades. The cortical network supporting the generation of reflexive saccade includes: (1) the primary and secondary visual cortices (V1, V2), which are involved in the generation of the saccades, since the stimulation of these regions can elicit saccades [119]; V1 and V2 also mediate the detection of motion and the direction of a moving target [173, 174]; (2) the

parietal eye fields (PEF), which disengage fixation and trigger reflexive saccades [106]; (3) the frontal eye fields (FEF), which, like PEF, have a role in fixation disengagement [175], although more recent findings suggest that FEF also accounts for performing accurate saccades [4, 176]; and (4) the supplementary eye fields (SEF), which are located on the border of the supplementary motor area (SMA) and the pre-supplementary motor area (pre-SMA) [177]; the role of the SEF in the execution of saccades was revealed by Tehovnik et al. [178] who demonstrated that stimulation of the SEF can elicit saccades. The research on reflexive saccade-related activity also revealed subcortical regions accounting for the generation of reflexive saccades: (1) the cerebellum; (2) the striatum; (3) the paramedian pontine reticular formation (PPRF); and (4) the superior colliculi (SC). However, given the aim of the present study, which focuses on the cortical network engaged in the preparation and execution of eye movements, the subcortical structures engaged in the preparation of reflexive saccades are only briefly described. The cerebellum accounts for maintaining saccade accuracy [179], the striatum is involved in both saccade initiation and inhibition, while the PPRF encodes monocular commands for saccades. Finally, the SC seems to play a crucial role in fixation control and saccade generation per se. Neggers et al. [149] demonstrated that the SC elicits saccades and modulates the latency of saccades, as larger activity observed in the SC resulted in faster saccades whereas another study showed that the inactivation of the SC caused deficits in saccade target selection [150].

Interestingly, Schiller et al. [119, 180] proposed that two processing streams – anterior and posterior – control reflexive saccades. The anterior stream includes FEF and SEF, and reaches the brainstem directly while bypassing SC, whereas the posterior stream includes the parietal and occipital cortex and accesses the brainstem through the SC. This division also relates to the different functional roles that these streams play, since the posterior stream is thought to mediate the generation of saccades, while the anterior system would select the target of the saccade.

In everyday life, we regularly perform vergences, as we constantly have to direct our gaze into different depths. A proper visual exploration regularly requires performing combined eye movements, in which both saccadic and vergence components can be distinguished. Even though vergences are essential for 3D perception, the involved neural pathways, both cortical and subcortical, are unclear as research on vergences is scarce. Two types of cues are well known for their capability to elicit vergences: the blur of an image, and binocular retinal disparity. The latter is considered to be a crucial factor for

triggering vergences [1]. The earliest studies on vergences focused on brain areas that process information about retinal disparity. Disparity-tuned cells have been found in V1 and V2 [158], and in subcortical (superficial layers of SC) [159] areas of a cats brain. Likewise, disparity detectors were also identified in the visual cortices (V1, V2, and V3) of primates [155, 156, 157]. Moreover, micro stimulation and single-neuron studies [181] showed that the rostral part of the SC generates information that accurately keeps the eyes in 3D position.

A recent study on humans using TMS [136] also demonstrated that the FEF are engaged in the execution of memory guided (i.e., endogenous) vergences. However, the results of EEG and fMRI studies indicated that a region of the frontal cortex located anterior to the saccade-related FEF may be involved in both volitional [167] and reflexive [154] vergences. Moreover, Gamlin and Yoon (2000) revealed that activation of an area anterior to the FEF (including the area between the arcuate sulcus and the posterior pole of the principal sulcus) is related to motoric aspects of vergence preparation, but not to sensory aspects, i.e. the detection of retinal disparity [167].

Studies using neuroimaging methods like PET and fMRI imply a high spatial resolution, but also a low temporal resolution. As a consequence, the transient activity of specific brain areas can easily be missed. Furthermore, the temporal sequence of the involved cortical brain areas remains rather obscure. Due to its high temporal resolution, EEG may provide important features of the temporal dynamics of the variously involved cortical mechanisms. According to our knowledge, only two EEG studies on vergences in humans have been published [160, 161]. Both studies explored the cortical mechanisms associated with reflexive eye movements: pure saccades, pure vergences, and combined vergences. These studies employed different paradigms and analyzed their data in a different way. Kapoula et al. (2002) investigated response-locked brain activity just before eye movement execution [160]. More negativity was observed preceding pure divergences than preceding pure convergences. Similarly, for combined divergences more negativity was observed than for combined convergences. Methodological restrictions (a small number of participants, a limited number of electrodes, and few trials per condition) did not allow them to determine the cortical topography associated with vergences. Nevertheless, their findings suggest that frontal and parietal areas are involved preceding the execution of vergences. In turn, Tzelepi et al. (2004) examined stimulus-locked brain activity after the onset of a relevant stimulus, so they focused on the sensory aspects of eye movement control [161]. They observed that convergences were preceded

by more negativity, which seemed more related to the N1 component, than divergences. Although both studies investigated cortical activity related to vergences, their results cannot easily be compared. Stimulus-locked analyses in the study of Tzelepi et al. (2014) predominantly reveals the processing of the stimulus that elicits eye movements, while response-locked analyses, as reported in the study of Kapoula et al. (2002) emphasizes the activity related to the execution of eye movements. Furthermore, the results of these studies can also not easily be considered as complementary, since the experimental design and setup were not the same.

In the current study, we tried to determine the cortical areas related to the execution of exogenous vergences, and additionally attempted to specify the possible roles of these areas. As a comparison of ERP topographies related to the execution of the different eye movements may be quite cumbersome and may not lead to clear conclusions we thought it might be more useful to describe the ERPs in terms of the activities of different underlying cortical sources. We used the BESA (brain electrical source algorithm) method, which enables to describe ERPs by different cortical sources with different activity patterns over time. The outcome of these analyses may also provide relevant information about the possible interplay between different cortical areas. Initially, we compared a response-locked activity for the different eye movement types as this may clarify whether a specific area is more relevant for a specific type of eye movement. Secondly, we compared a response-locked and stimulus-locked activity. The differences between these activities may indicate whether the underlying process is more related to eye movement execution or to processing the target of the eye movement.

2.2. MATERIAL AND METHODS

2.2.1. PARTICIPANTS

Sixteen healthy volunteers (12 females and 4 males) with an average age of 22.6 years (SD = 0.7) participated in this study. Two of them were excluded from the analyses since in both cases over 40% of their eye movements were accompanied by blinks, which makes a proper assessment of eye movement onset problematic. All participants reported being right-handed. None of the participants had a history of any neurological or psychiatric disorders.

The study was approved by the local ethics committee of the Adam Mickiewicz University and was performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from all of the participants.

2.2.2. OPTOMETRIC EXAMINATIONS

All participants took part in an optometric examination session. The administered test measured refractive errors and monocular distance and near visual acuity (Snellen's letter chart) with corrected refractive errors. Subsequently, the following parameters of binocular vision were measured: (1) distance and near heterophoria using a cover test with a prism bar, (2) fusional vergence ranges using a prism bar, (3) suppression using a Worth 4-dot test and a Pola Mirror test, (4) the near point of convergence (NPC) measured by a push-up method (5) and stereopsis, by using the Paul Harris Randot Test (Stereo Optical©).

Optometric eye examinations revealed that the visual acuity of both eyes of participant's eyes was in a normal range for near and far space (logMAR $\leq$ 0.00). In some cases, refractive errors were corrected by glasses or contact lenses (participants with contact lenses were included only when they used this correction on a daily basis). None of the subjects presented any suppression and all achieved at least 30 sec of arc in the stereopsis test. Far heterophoria ranged from 2 prism diopters of exophoria to orthophoria, whereas near heterophoria ranged from 6 prism diopters of exophoria to 1 prism diopters of esophoria. The averaged values of the fusional vergence ranges and near point of convergence (break and recovery) are listed in Table 2, whereas measured parameters for each participant are presented in the Supporting Information section.

Table 2. Averaged clinical parameters of optometric examination for positive (base-out) and negative (base in) fusional range, the break and recovery point of near point of convergence.

Parameter	Averaged values
Positive fusional range at far (prdptr)	18.7 ± 4.8
Negative fusional range at far (prdptr)	8.5 ± 1.4
Positive fusional range at near (prdptr)	26.6 ± 6.2
Negative fusional range at near (prdptr)	16.1 ± 3.2
Near point of convergence – break (cm)	3.4 ± 1.7
Near point of convergence – recovery (cm)	4.8 ± 1.9

2.2.3. TASK AND STIMULI

All stimuli were displayed on a device with LEDs located at various positions (see Fig. 13). Six LEDs were positioned at the eye level on isovergent circles at far and near visual space: 1 m and 20 cm from the center of eye rotation (located 2.5 cm from the nasal bridge), respectively. The lateral separation of LEDs was 10˚, so the stimuli triggering pure saccades produced zero retinal disparity, whereas stimuli triggering both vergence eye movements produced 12˚ disparity (both crossed and uncrossed). Moreover, the lateral separation was adjusted and based on a previous study [182] which showed that below 15° saccades do not require head movements and are more natural. The chin and forehead were stabilized to exclude head movements, which would disrupt EEG and electrooculographic (EOG) signals. Three main types of eye movement were elicited: pure saccades for far and near positions, combined convergences, and combined divergences. Each type of eye movement to the right and to the left LED had to be carried out 51 times, resulting in a total of 408 trials in the experiment. The three blocks of 136 trials, which were presented in a counterbalanced order, were separated by ten-minute breaks. The experiment was preceded by a demo block, which consisted of all the eight different eye movement types, which were repeated five times and were presented in a random order. Eye movements (EOG signal) were monitored online to ensure that participants performed the task in line with the instructions.

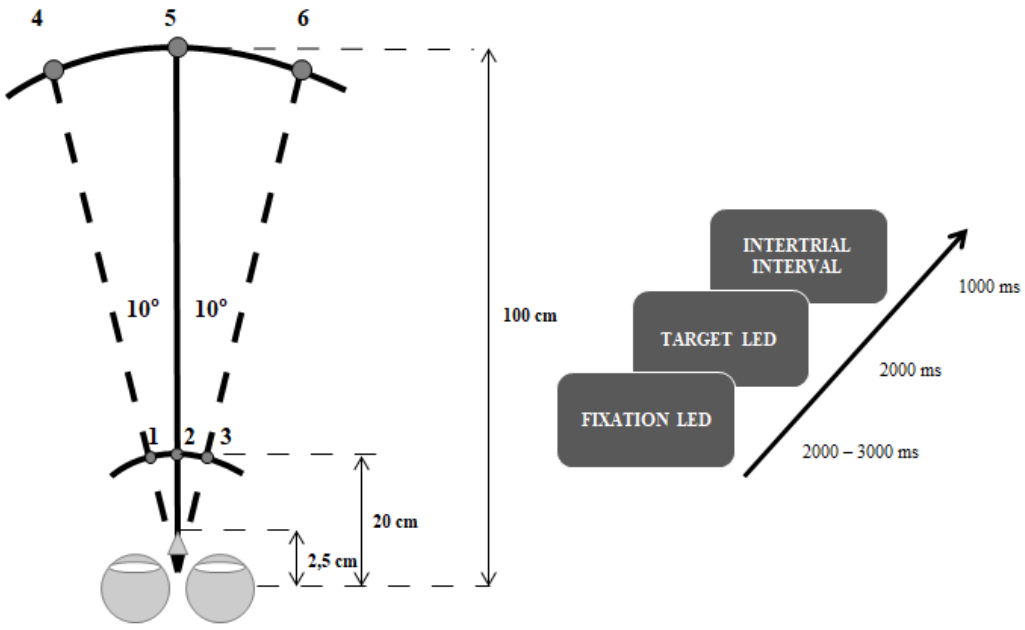

Fig. 13. A) A graphical representation of the experimental setup. LEDs (light-emitting diodes) were placed at eye level on isovergent circles at two distances from the observer: 20 cm and 100 cm. Eye movements were elicited for both distances, depending on the combination of the fixation and the target LED. Each trial started with the onset of the fixation LED in the midline (position 2 or 5) which was followed by the onset of one of the lateral target LEDs. Eye movements were triggered by redirecting the eyes as following: saccades at far – from LED 5 to LED 4 (leftward saccades) or 6 (rightward saccades); saccades at near – from LED 2 to LED 1 (leftward saccades) or 3 (rightward saccades); combined convergences – from LED 5 to LED 1 (leftward combined convergences) or 3 (rightward combined convergences); combined divergences – from LED 2 to LED 4 (leftward combined divergences) or 6 (rightward combined divergences). **B) The design of the experiment as a function of time.** Each trial started with the fixation LED, displayed for a random duration between 2,000 to 3,000 Subsequently the target LED was presented for 2,000 ms, which was followed by a 1,000-ms intertrial interval.

Each trial started with the onset of the fixation LED at the near or far position in the midline (LED 2 or 5 in Fig. 13A). The fixation LED was presented for a random duration between 2,000 to 3,000 ms in 50 ms steps to reduce temporal anticipation. The fixation LED was followed by the onset of one of the lateral target LEDs which was displayed for 2,000 ms. The design of the experiment in the function of time is presented in Fig. 13B.

The experiment was carried out in a completely darkened room. Participants could only see the LED that they had to fixate on. The brightness of the LEDs was controlled and individually adjusted so that the near and the far LEDs were perceived as equally bright. The size of the LEDs was also adjusted depending on their distance: near LEDs

(0.3 cm) were smaller than far LEDs (1.2 cm) in such a way that they stimulated a similar size of the retina.

Before the experiment started, verbal instructions were given. Participants were instructed to make an eye movement from the fixation LED to the target LED as quickly but also as accurately as possible. On average, the experimental part took approximately one hour per participant.

2.2.4. EEG RECORDINGS

The EEG was registered from 64 active electrodes placed on an actiCap (Brain Products GmbH) located on positions according to the extended International 10-20 system [55]. A ground electrode was affixed at AFz. An average reference was used. Electrode resistance was kept below 5 kΩ. The signal was amplified by a QuickAmp 128 amplifier (Brain Products GmbH) with a sample rate of 500 Hz, and was filtered online with a low cut-off filter of 0.015 Hz to remove slow drifts possibly related to small head movements.

Eye movements and blinks were recorded by measuring the EOG from three bipolar electrodes (Fig. 14): one of them was located above and below the right eye (for vertical eye movement and blink detection – vEOG) and two other electrodes were mounted on the outer and inner canthi of both the right and the left eyes (for horizontal eye movement detection – $hEOG_{right}$, $hEOG_{left}$). The EOG was filtered with low cut-off (0.25 Hz) and high cut-off filters (30 Hz). EEG, EOG, and digital markers signaling relevant events in the experiment were registered with a Brain Vision Recorder (Brain Products GmbH). The EOG and EEG signals were analyzed offline with Brain Vision Analyzer 2.0.3 (Brain Products GmbH) software.

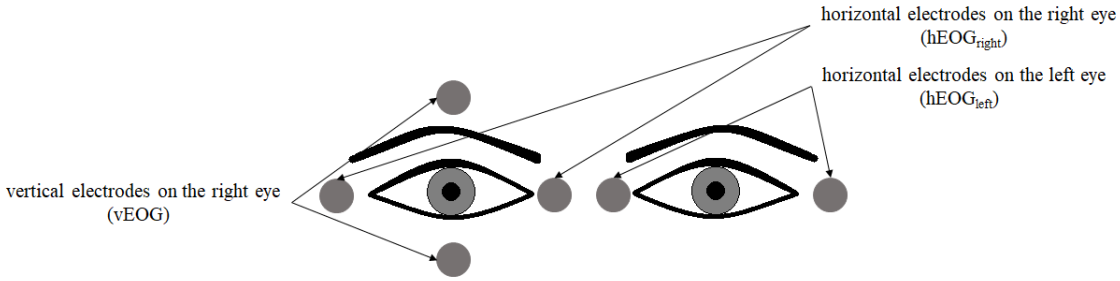

Fig. 14. Electrode placement for EOG data collection. First, the saccade signal was registered separately for left and right eyes. Subsequently, they were averaged using the following formula: $EOG_{sacc} = (hEOG_{left} + hEOG_{right})/2$.

2.2.5. BEHAVIORAL ANALYSES

Every eye movement elicited in this study contains a saccadic component. The onset and peak of the registered eye movement were marked on the saccade signal (EOG_{sacc}). The saccade signal was initially determined using the following formula: $EOG_{sacc} = (hEOG_{left} + hEOG_{right})/2$, to eliminate differences between the left and right eye [183]. The onset and peak of each eye movement was determined on a trial by trial basis using the EMG onset search algorithm (implemented in the Brain Vision Analyzer version 2.0.4.). The onset of an eye movement has been defined as follows: the mean amplitude and its standard deviation are calculated for a baseline period (0 - 100 ms). The onset criterion is subsequently set to a quintuple of the SD above or below the mean, depending on its polarity. Thus, the implemented solution searches for the time point at which EMG activity exceeds 5 SD from the mean of the baseline period. Trials with improper eye movements, which was based on an additional thorough visual inspection, were excluded from further analyses. Based on the determined eye movement onset, latencies can be defined as the time interval from stimulus onset to eye movement onset. The following exclusion criteria were used: incorrect direction, premature onset (< 100ms), and too slow onset (> 600ms). We chose the latter criterion as eye movements slower than 600 ms appear not to be exogenously triggered. Eye movements accompanied or preceded by eye blinks were additionally excluded. In total, the number of removed segments amounted to 9.40 %.

2.2.6. EEG ANALYSES

Segments from -400 to 400 ms relative to eye movement onset were extracted from the raw EEG data, which were large enough to be able to perform both response-locked and stimulus-locked analyses. After application of the behavioral exclusion criteria, an artifact rejection procedure was performed: trials with major artifacts were excluded from any further analyses (maximum allowed voltage step: 100 μV/ms, lowest allowed activity within 50 ms intervals: 0.1 μV). Subsequently, we corrected for artifacts of non-cortical sources (e.g., muscle artifacts, electrocardiac artifacts etc.) by employing the semiautomatic Independent Component Analysis (ICA) algorithm. The average number of removed components amounted to 1.8. After application of the ICA procedure, the artifact rejection procedure was repeated with more strict criteria (maximum allowed voltage step: 50 μV/ms, minimum/maximum allowed amplitude: ±150 μV, maximum

allowed difference of values within 200 ms intervals: 200 μV). The artifact rejection procedures carried out before and after ICA resulted in the removal of less than 1 % of the data. Subsequently, averages were computed for each condition and each electrode.

To minimize the possibility that the observed activity reflects eye movement execution, we restricted our analyses to a -180 to -60 ms time interval. In this time interval, motoric aspects of eye movement preparation were investigated. The selected interval was based on the longest observed average latency (179 ms for leftward combined convergences, see the Results section). Including earlier time windows might reflect activity related to the fixation LED, which appeared before the target LED. To enable a comparison of the response- and stimulus-locked activity, an appropriate time interval had to be selected for the stimulus-locked analyses. To avoid interference from subsequent eye movements, we based our selection on the latency of the saccades, which had the shortest latencies (see the Results section). This latency (135 ms) determined the last analyzed time interval (120 - 140 ms relative to the stimulus). The length of the time interval for stimulus-locked analyses was chosen to be the same as for the response-locked analyses, i.e. 120 ms. Therefore, we selected the time interval from 20 to 140 ms after stimulus onset.

2.2.7. SOURCE ANALYSIS METHOD

BESA software (version 6.0, MEGIS Software GmbH) was used to localize the cortical generators related to the preparation and execution of the different eye movement types. All 64 channels were included in the analyses. The cortical activation underlying the ERPs may be described by current dipoles [184] or by regional sources [185, 186]. We decided to use regional sources as they have been reported to create more stable models [86].

The locations of the regional sources of the observed scalp potentials were determined for the time range from -180 to -60 ms before eye movement onset using the BESA algorithm. A PCA of the grand averages per condition revealed that three symmetrical regional source pairs should be sufficient to describe 99.2 % of the data. The global field power (GFP) of the grand average was used to identify relevant time windows, which were selected from the onset of the peak of the GFP to its local maximum. The fitting procedure was sequentially applied for the relevant time windows, and one or more symmetrical source pairs were inserted to describe activity in each time

window. The aim of the fitting procedure was to find a best-fit solution that minimizes the residual variance (RV). We assumed that the same areas are involved in all eye movement types but that these areas are involved in different degrees. Initially, a model was built and based on the ERPs averaged across all types of eye movements and participants. One symmetrical source pair was fitted to each of the relevant time windows i.e. (1) -180 to -154 ms, (2) -130 to -60 ms. This model described the preparation of saccades and combined divergences quite well, resulting in the low values of RV. However, it seemed insufficient to properly describe combined convergences (RV=8%). Adding a second source pair in each relevant time window resulted in a decrease of RV. However, we intended to obtain a similarly low RV value with three pairs of regional sources for all conditions, since a PCA of the grand averages showed that a model with three regional pairs should be sufficient to describe the observed data. Therefore, we decided to determine the regional sources for the grand averages of combined convergence. Here, three relevant time windows were identified: (1) -180 to -154 ms, (2) -132 to -96 ms, and (3) -86 to -60 ms. One symmetrical source pair was fitted to each time interval, resulting in a significant reduction of the RV. Adding more sources did not further reduce RV. As a final check, we also examined a model based on fMRI data from a study by Alkan et al. (2011) [154]. Even though this model included a larger number of sources it did not result in a solution with lower RV, so it is obviously less parsimonious. Based on these examinations, we decided to use the model with three regional sources.

Source activities were estimated by applying the selected model on the ERPs for each type of eye movement per participant [187, 188]. Subsequently, the root-mean-square (RMS) values for each separate source was determined, which creates an estimate of overall source activity [40]. This procedure was applied for each participant, and each type of eye movement. The acquired data was subsequently used for the statistical analyses.

2.2.8. STATISTICAL ANALYSES

For the statistical analyses, STATISTICA 12 software was used. The onset latencies of the eye movements were evaluated by an analysis of variances (ANOVAs) with repeated measures with two factors: *eye movement type* (saccades, combined convergences, and combined divergences) and *direction* of the eye movement (right or left).

The statistical analyses of RMS for a response-locked activity were carried out on 20-ms intervals from -180 to -60 ms before saccade onset to examine the preparation of the different exogenous eye movement types (Fig. 15). Although we removed all trials with detectable premature eye movements, to check whether observed cortical activity is not due to eye movement execution the dependency between EOG and the estimated source activities was examined. We used Pearson's correlation coefficient, *r*, and correlated the estimated source activities with the EOG. For saccades we used EOG_{sacc} (determined above), while for vergences we used EOG_{verg} (calculated using the following formula: $EOG_{verg} = (hEOG_{left} - hEOG_{right})$). Since in the case of vergences, the eyes move in opposite directions, we calculated the difference between horizontal movements of the left and right eye rather than the average.

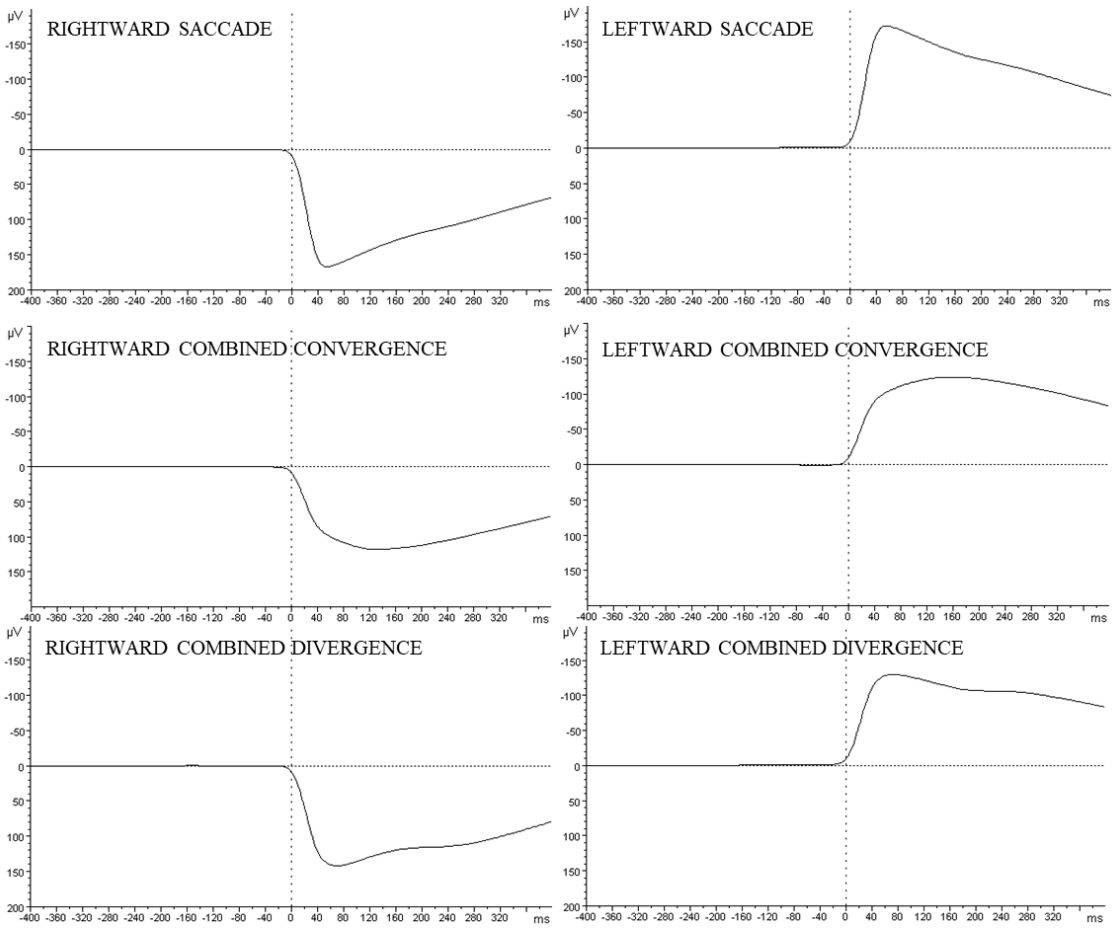

Fig. 15. Electro-oculographic (EOG) signals measured from the electrodes attached to the outer and inner canthi of both the right and the left eyes. The grand averages, based on 14 participants, are presented for each condition from -400 to 400 ms relative to the saccade onset of each eye movement.

The statistical analyses of response-locked source activities were carried out by using a repeated measures ANOVA with the following factors: *source* (RS1, RS2, RS3),

time (six 20-ms time windows starting from -180 ms to -60 ms relative to eye movement onset), *eye movement type* (saccades, combined convergences and combined divergences), *direction* (to the right or to the left), and *hemisphere* in which the source was located (left or right). However, to enable an interpretation of several complex significant interactions, we also performed ANOVAs for each regional source separately.

To compare response-locked and stimulus-locked data, a repeated measures ANOVA was performed with the factors: *time* (six 20-ms time windows), *event* (stimulus- or response-locked), and *eye movement type* (saccades, combined convergences and combined divergences). To reduce the complexity of the analyses, we computed averages across rightward and leftward eye movements, which were subjected to the analyses.

To be able to properly interpret possible activity differences within the most posterior source, we additionally compared stimulus-locked contralateral activities between eye movement types for this source. To calculate the contralateral activity, activity after right LEDs within left and activity after left LEDs within right posterior sources were averaged. Different activities for each condition shortly after stimulus onset (at 100 ms) might imply that initial processing already depends on the information to be extracted. The statistical analyses included the following factors: *time* (six 20-ms time windows starting from 20 ms to 140 ms relative to stimulus onset), and *eye movement type* (saccades, combined convergences and combined divergences).

For all of the employed analyses, significance was assigned at the $p \leq 0.05$ level. ANOVAs were followed by Tukey's posthoc tests, and Huynh – Feldt ε correction was performed when necessary.

2.3. RESULTS

2.3.1. BEHAVIORAL DATA

Eye movement onset latencies are presented in Table 3. Saccades were characterized by the shortest mean onset latencies, intermediate latencies were obtained for combined divergences, and the longest latencies were observed for combined convergences. ANOVA confirmed the presence of a major effect of *eye movement type* ($F(2,26) = 75.2$, $p < 0.001$, $\eta^2 = 0.65$). Post-hoc tests revealed that saccades were faster than combined divergences ($p < 0.001$); and combined divergences were faster than

combined convergences ($p < 0.001$). The analysis revealed that latencies were not dependent on the direction of the eye movements, since there was no main effect of *direction* ($F(1,13) < 0.01$, $p = 0.953$, $\eta^2 < 0.001$), and also no *eye movement type* x *direction* interaction ($F(2,26) = 0.02$, $p = 0.943$, $\eta^2 = 0.001$).

Table 3. Mean latencies for exogenously triggered saccades, divergences, and convergences based on 14 participants. SE represents the standard error.

Eye movement type		Latency [ms]	SE [ms]
Saccades	Rightward	136	5
	Leftward	135	6
Divergences	Rightward	154	5
	Leftward	153	5
Convergences	Rightward	178	6
	Leftward	179	8

Source analyses revealed that the following cortical areas are strongly related to the execution of the different eye movement types (for details see the Source analysis section): (RS1) an anterior frontal area, (RS2) the occipital cortex, and (RS3) the FEF.

The analyses showed that in the -100 to -80 ms time interval, for RS1 significant correlations were observed for rightward combined convergence between right RS1 and EOG_{verg} ($p = 0.001$), and left RS1 and EOG_{verg} ($p = 0.003$). Significant correlations were observed also for leftward combined convergence between right RS1 and EOG_{verg} ($p = 0.045$). In the next time interval -80 to -60 ms significant correlations were observed for rightward combined convergence between right RS1 and EOG_{verg} ($p = 0.032$). For sources located within the left and right RS2 no significant correlation was observed in both -100 to -80 ms (EOG_{sacc} $p \geq 0.137$, EOG_{verg} $p \geq 0.108$) and -80 to -60 ms time intervals (EOG_{sacc} $p \geq 0.082$, EOG_{verg} $p \geq 0.283$). For RS3 a significant correlation was observed in the -100 to -80 ms time interval, whereas in the subsequent time window no significant correlation was observed (EOG_{sacc} $p \geq 0.062$, EOG_{verg} $p \geq 0.084$).

Based on these results, it may be concluded that the activity of RS1 reflects a residual eye movement artifact (see Discussion), whereas correlations observed for RS3

seem due to chance effects as no consistent pattern of correlations was observed over time. Specifically, if these correlations were induced by eye movements, similar correlations should have been observed for subsequent time windows.

2.3.2. EVENT RELATED POTENTIALS

The topographical maps of the grand averages of ERPs showing cortical activity from -180 to -60 ms relative to eye movement onset for the different eye movement types are displayed in Fig. 16, whereas the grand average waveforms of ERPs for representative electrodes are shown in Fig. 17. As indicated above, we focused on the source analysis results and used the grand averages of ERPs to prepare the model.

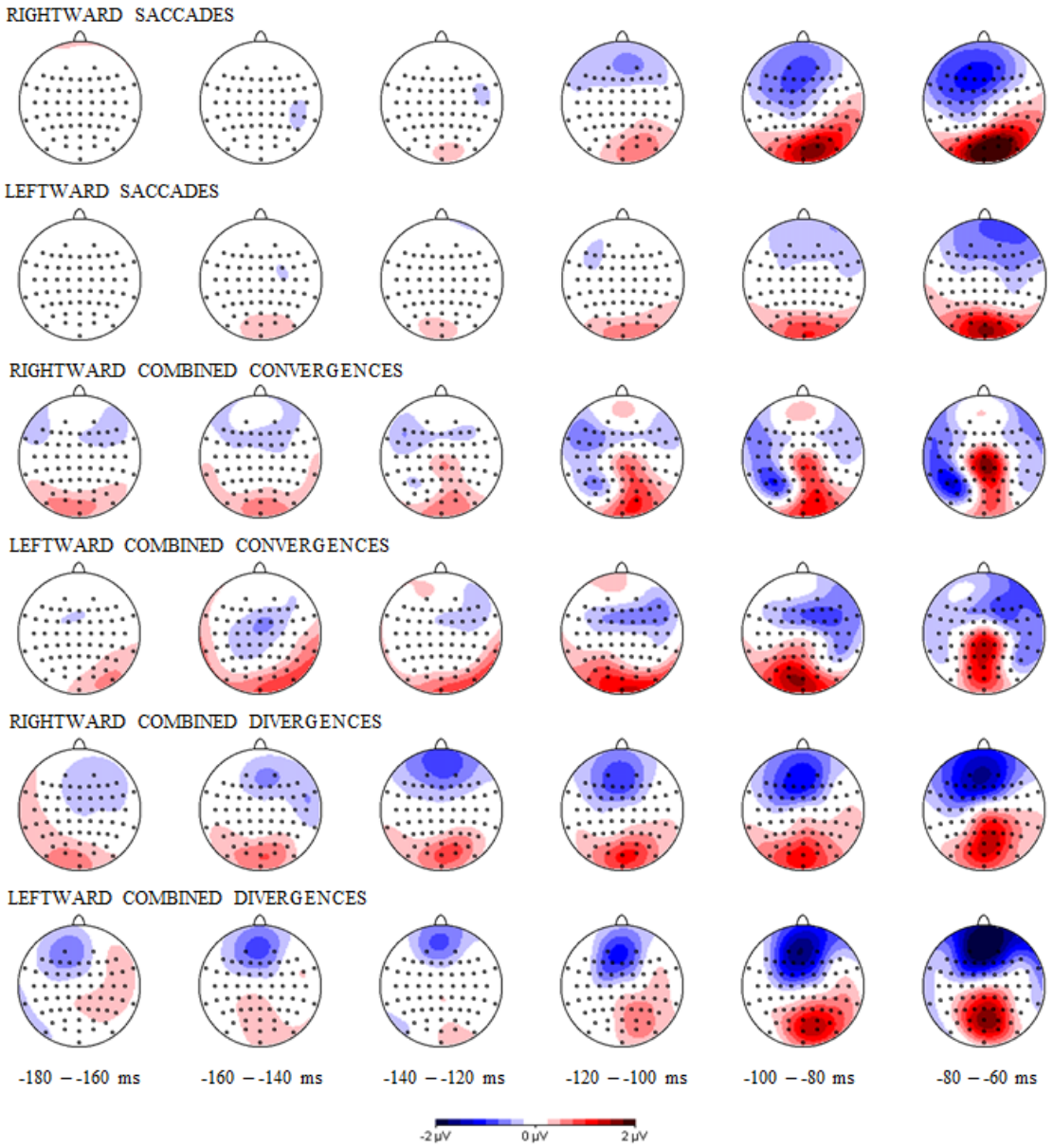

Fig. 16. Topographical maps of event-related potentials for the three eye movement types from -180 ms to -60 ms before eye movement onset. The first two rows display the maps for pure left and right saccades, the third and fourth row show the maps for combined left and right convergences, and the two lower rows represent the maps for left and right combined divergences.

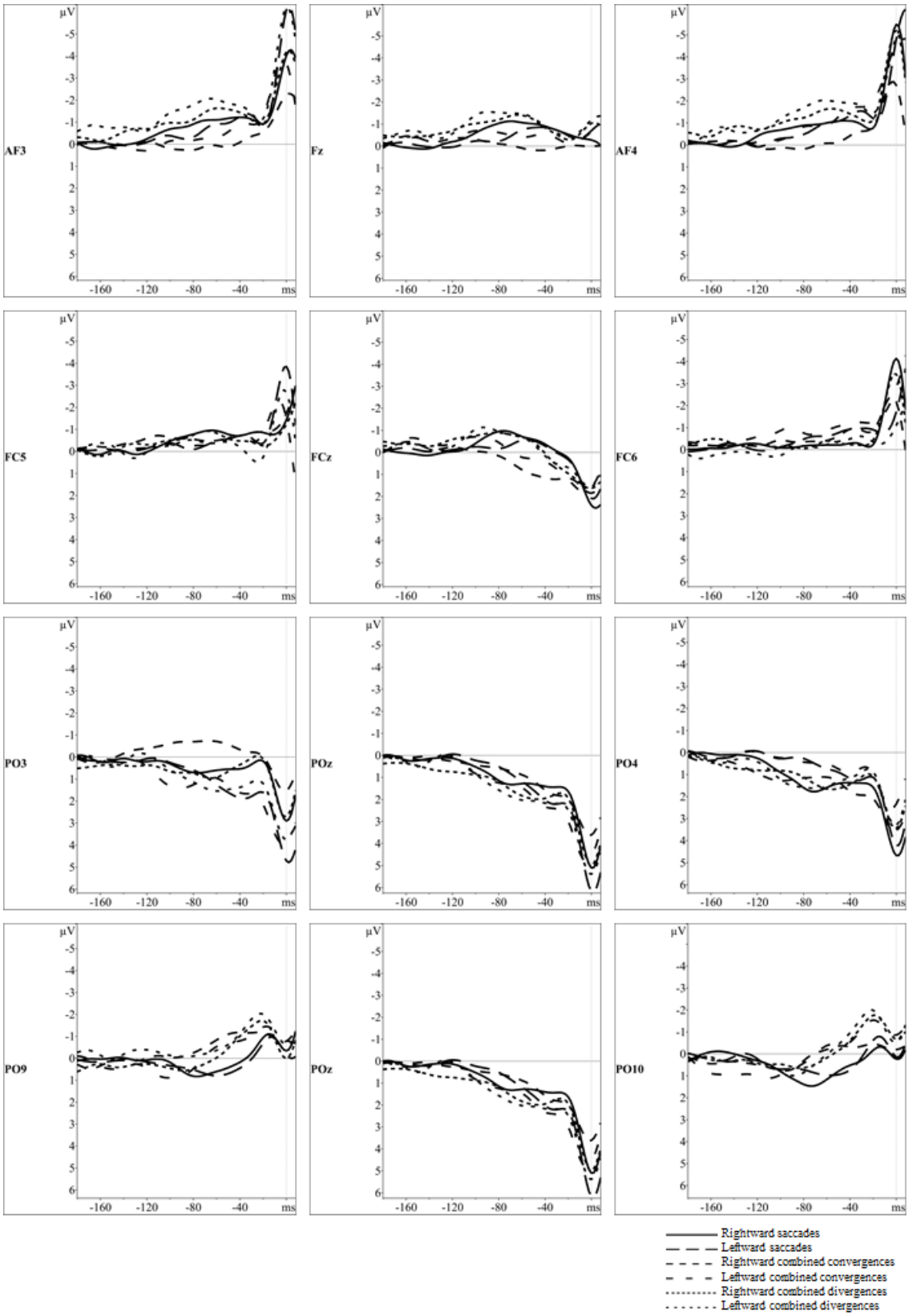

Fig. 17. Grand average waveforms of event related potentials for three eye movement types in time intervals from -180 ms to 10 ms relative to eye movement onset. The grand averages waveforms of the response-locked activity are presented for 12 relevant electrodes located in the frontal, parieto-occipital and occipital cortex.

2.3.3. SOURCE ACTIVITIES

A PCA on the obtained grand averages indicated that RV may be substantially reduced, up to 1.81%, when using three regional sources. Based on inspection of the GFP we decided that the fitting procedure should be performed for the following three time windows selected from the onset of a peak to the local maximum of the GFP. Each regional source (RS) pair was fitted to a subsequent time interval, i.e. RS1 to the -180 to -154 ms time window, RS2 to the -132 to -96 ms time window and RS3 to the -86 to -60 ms time window. In Fig. 18, a model is presented displaying the estimated locations of the different regional source pairs.

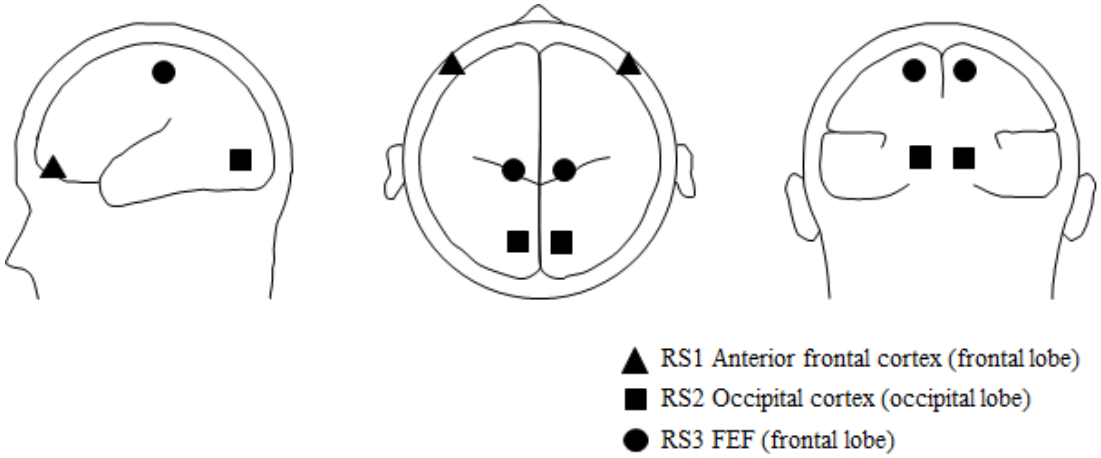

Fig. 18. Estimated pairs of source locations based on event-related potentials (ERPs) observed preceding lateral exogenous saccades, convergences, and divergences. A model was built based on the averaged ERPs obtained for combined convergences using the BESA algorithm. Based on the GFP inspection, the fitting procedure was performed for the three time windows selected from the onset of a peak to the local maximum of the GFP: (1) -180 to -154 ms, (2) -132 to -96 ms, and (3) -86 to -60 ms. Three pairs of regional sources (RS) were fitted to subsequent time intervals: RS1, RS2, and RS3, respectively.

The obtained RV amounted to 1.56% for the saccade condition, 4.82% for the combined convergence condition, and 2.78% for the combined divergence condition. The regional sources that seem related with the execution of the different eye movement types are located in: (RS1) an anterior frontal area (the frontal lobe), (RS2) the occipital cortex (the occipital lobe), and (RS3) the FEF (the frontal lobe). Precise locations of the regional sources, in terms of Brodmann areas and Talairach-Tournoux coordinates, are indicated in Table 4. Anatomical regions were determined using the Talairach Client software (version 2.4.3), using Single Point Search [189]. As mentioned in the Materials and

Methods section, we also examined models with a different number of sources, however, the chosen model with three pairs of symmetrical regional sources described activity preceding the eye movements in the most optimal way, as an increase in the number of sources did not substantially reduce RV and a reduction in the number of symmetrical sources substantially increased RV (>8%).

Table 4. Talairach coordinates of regional sources related to the execution of saccades, convergences, and divergences. The regional sources were determined for the time window -180 ms to -60 ms before the eye movement onset. A model was built and based on the averaged ERPs obtained for combined convergences using the BESA algorithm. Cortical regions were estimated using the Talairach Client software (version 2.4.3).

Regional sources	Fitting time intervals	Cortical region	Brodmann Area	X	Y	Z
RS1	-180 to -154 ms	Anterior frontal cortex	**10**	**+/-53**	**57**	**0**
RS2	-132 to -96 ms	Occipital cortex	**18**	**+/-12**	**-81**	**-5**
RS3	-86 to -60 ms	Frontal eye field	**6**	**+/-13**	**-31**	**55**

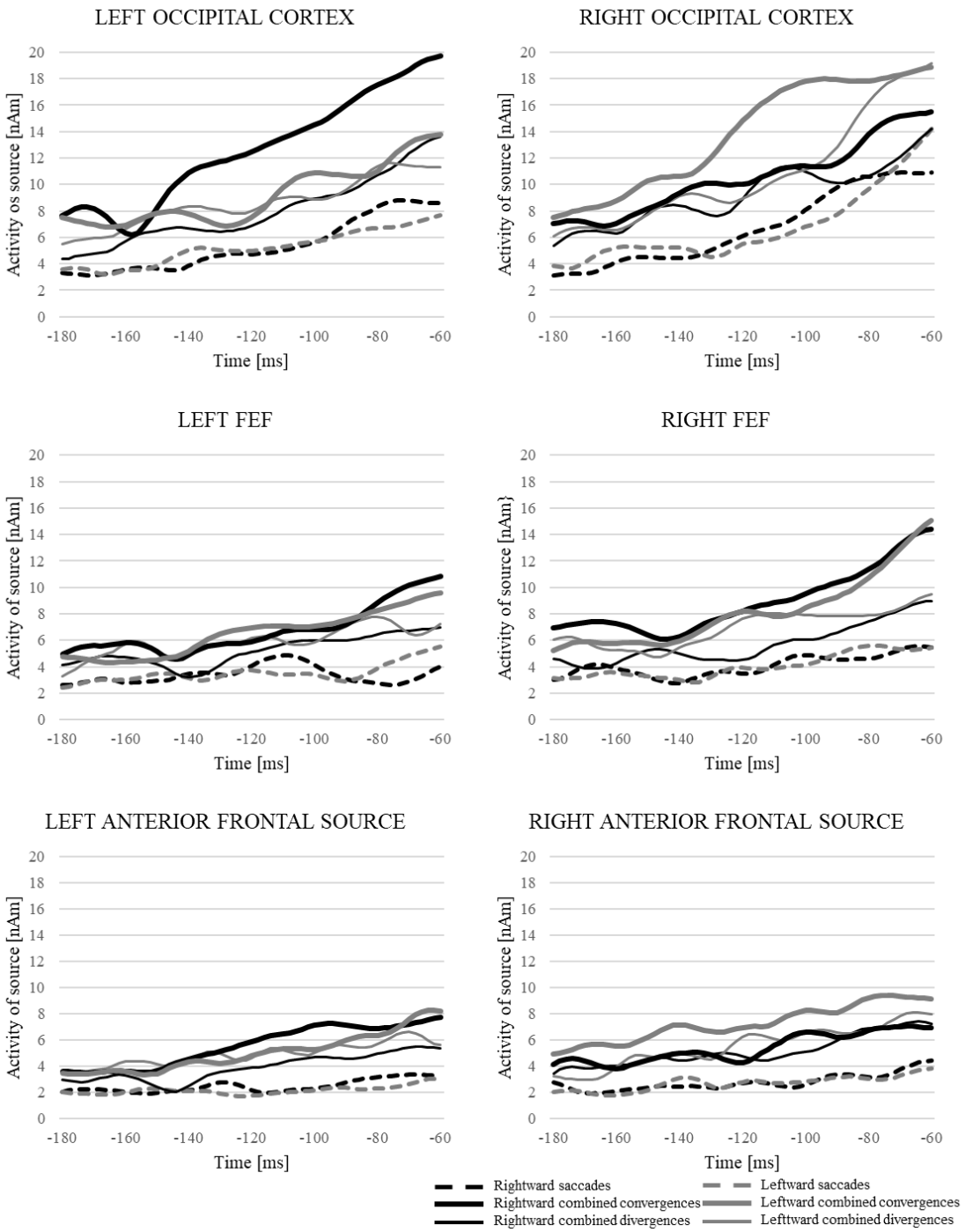

Fig. 19. Source waveforms elicited by activity preceding the different eye movement types for each regional source. Source waveforms were prepared per participant by calculating the RMS (root mean square) for each condition within each of the three regional sources per hemisphere. Then, the averages of all individuals per condition were computed, the result of which is shown in the figure. The obtained individual averages for each type of eye movement per condition were used for statistical analyses.

Overall, we observed a significant main effect of *source* ($F(2,26) = 23.6$, $p < 0.001$ $\eta^2 = 0.64$). Post-hoc tests revealed that activity was larger in RS2 than in RS3 ($p < 0.001$) and larger in RS2 than in RS1 ($p < 0.001$). No difference in activity was observed between

RS1 and RS3 (p = 0.13). The analyses performed for each regional source separately showed that activity differed over time, being largest shortly before eye movement onset for RS2 (main effect of *time*, for RS2 (F(6,65) = 30.6, p < 0.001, η^2 = 0.70)), for RS3 (main effect of *time* (F(6,65) = 29.2, p < 0.001, η^2 = 0.69)) and for RS1 (main effect of *time* (F(6,65) = 15.8, p < 0.001, η^2 = 0.55)). A contrast analysis revealed a linear trend (for RS2 (F(1,13) = 37.1, p < 0.001), for RS3 (F(1,13) = 42.8, p < 0.001)) and for RS1 (F(1,13) = 19.1, p < 0.001)). Fig. 19 suggests that these effects reflected a general increase in source activity. Source activity was also larger for right hemispheric than for left hemispheric sources for RS2 (main effect of *hemisphere* (F(1,13) = 7.1, p = 0.02, η^2 = 0.35)), RS3 (main effect of *hemisphere* (F(1,13) = 15.1, p = 0.002, η^2 = 0.54)) and RS1 (main effect of *hemisphere* (F(1,13) = 9, p = 0.01, η^2 = 0.41)).

2.3.3.1. OCCIPITAL CORTEX (RS2)

For RS2, analysis of the source activities revealed a main effect of *eye movement type*, F(2,26) = 30.1, p < 0.001, η^2 = 0.70). This effect concerned differences between all *eye movement types*: saccades vs. combined convergences (p < 0.001), saccades vs. combined divergences (p < 0.001), and combined convergences vs. combined divergences (p = 0.007). As can be noticed in Fig 7, the largest activity was observed prior to combined convergences, intermediate prior to combined divergences, and the lowest prior to saccades. Additionally, a significant interaction between *direction* and *hemisphere* (F(1,13) = 5.3, p = 0.04, η^2 = 0.29) was observed. Post-hoc tests revealed that the hemispherical differences only concerned leftward eye movements, which elicited the strongest activity in the right hemisphere (p = 0.02). We did not observe similar results for rightward eye movements (p > 0.05).

A significant interaction between *eye movement type, direction,* and *hemisphere* (F(2,26) = 11.1, p = 0.002, η^2 = 0.46) was observed. Furthermore, interaction between *eye movement type*, *direction*, *hemisphere* and *time* was found (F(10,130) = 3.6, p = 0.002, η^2 = 0.21). To enable an interpretation of these complex interactions, we performed ANOVAs for each type of eye movement.

For saccades the interaction between *direction* and *hemisphere* (F(1,13) = 0.03, p = 0.875, η^2 < 0.01) as well as the interaction between *direction*, *hemisphere* and *time* was insignificant (F(5,65) = 2.4, p = 0.082, η^2 = 0.15). For combined divergences the interaction between *direction* and *hemisphere* was also insignificant (F(1,13) = 0.6, p = 0.448, η^2 = 0.04), but the interaction of these factors with *time* was in turn significant

($F(5,65) = 4$, $p = 0.012$, $\eta^2 = 0.24$). Post-hoc tests revealed that differences only concerned the last time window (-80 to -60ms), where within the right hemisphere rightward combined divergence was related to higher activity compared to leftward combined divergence ($p < 0.001$), and rightward combined divergence evoked higher activity in the right hemisphere, compared to the left hemisphere ($p < 0.001$). In turn, for combined convergences both interactions were significant (*direction* * *hemisphere* ($F(1,13) = 9.7$, $p = 0.008$, $\eta^2 = 0.43$); *direction*, *hemisphere* * *time* ($F(5,65) = 5.1$, $p = 0.005$, $\eta^2 = 0.28$)). Post-hoc tests performed for the *direction* and *hemisphere* interaction revealed that these differences were related to leftward combined convergences which evoked higher activity in the right RS2 compared with the left RS2 ($p = 0.042$). Moreover, the post-hoc test performed for *direction*, *hemisphere* and *time* interaction revealed that leftward combined convergence was related to higher activity in the right hemisphere ($p < 0.039$) in the time window -140 to -60 ms. Post-hoc tests also revealed that in the time window -120 to -80 ms within right RS2 leftward combined convergences evoked higher activity compared to rightward combined convergences ($p < 0.005$) and conversely – within left RS2 in time window -100 to -60 ms rightward combined convergences evoked higher activity compared to leftward combined convergences ($p < 0.02$).

2.3.3.2. FRONTAL EYE FIELD (RS3)

For RS3, a main effect of *eye movement type* was observed ($F(2,26) = 41.5$, $p < 0.001$, $\eta^2 = 0.76$). We observed differences between all conditions: saccades vs. combined convergences ($p < 0.001$), saccades vs. combined divergences ($p < 0.002$), and combined convergences vs. combined divergences ($p < 0.002$). The activity was the largest for combined convergences, lower for combined divergences, and lowest for saccades. The interaction between *eye movement type* and *time* revealed that the differences as a function of eye movement type was not constant ($F(2,26) = 41.5$, $p < 0.001$, $\eta^2 = 0.76$). The post-hoc tests revealed that a statistically significant difference between saccades and combined convergences ($p < 0.001$) was observed for all time intervals (-180 to -60 ms). In turn, the significant differences between saccades and combined divergences were only observed in the time window from -140 to -60 ms ($p < 0.001$), and the differences between the two combined vergence conditions were only observed shortly before eye movement onset (-100 to -60 ms) ($p \leq 0.027$).

2.3.3.3. ANTERIOR FRONTAL CORTEX (RS1)

Separate statistical analysis performed for RS1 showed significant differences in the level of activation between conditions ($F(2,26) = 9$, $p = 0.006$, $\eta^2 = 0.41$). The largest activity was observed for combined convergences and the smallest activity was found for saccades. Post-hoc tests disclosed that in the analyzed -180 to - 60 ms time window, activity of the source for combined convergence was larger than for saccades ($p = 0.001$), and activity for combined divergence was significantly larger than for saccades ($p = 0.018$). No differences were observed between both vergence conditions ($p = 0.479$). Here, we also observed that the direction of the eye movements influence the level of activity ($F(1,13) = 8.2$, $p = 0.013$, $\eta^2 = 0.39$). It was higher for left eye movements than for right eye movements ($p = 0.013$).

When the influence of the hemisphere was taken into account, no differences in the activity between eye movement types were observed (*direction * hemisphere* interaction ($F(1,13) = 3.3$, $p = 0.092$, $\eta^2 = 0.20$). Moreover, the differences between eye movements were not dependent on the direction of the eye movements (*eye movement type * direction* interaction $F(2,26) = 1.5$, $p = 0.246$, $\eta^2 = 0.10$) as well as time (*eye movement type * time* interaction, $F(10,130) = 1.4$, $p = 0.275$, $\eta^2 = 0.09$).

Separate analyses per eye movement type revealed that in RS1 the effect of lateralization was only observed for combined convergences (significant *direction * hemisphere* interaction $F(1,13) = 11.9$, $p = 0.004$, $\eta^2 = 0.48$). Post-hoc tests revealed that this lateralization effect was limited to leftward combined convergences, which elicited larger activity compared to the rightward combined convergence on the right hemisphere ($p = 0.011$), and to the leftward combined convergence which elicited higher activity in the right hemisphere compared to the left hemisphere ($p = 0.002$).

2.3.4. A COMPARISON OF RESPONSE-LOCKED AND STIMULUS-LOCKED ACTIVITIES

To be able to better interpret the observed source activities, we compared response-locked activity from -180 to -60 ms with stimulus-locked activity from 20 to 140 ms relative to target stimulus onset. In Fig. 20, a comparison of the response- and stimulus-locked activity is presented for saccades, combined convergences, and combined divergences for each regional source.

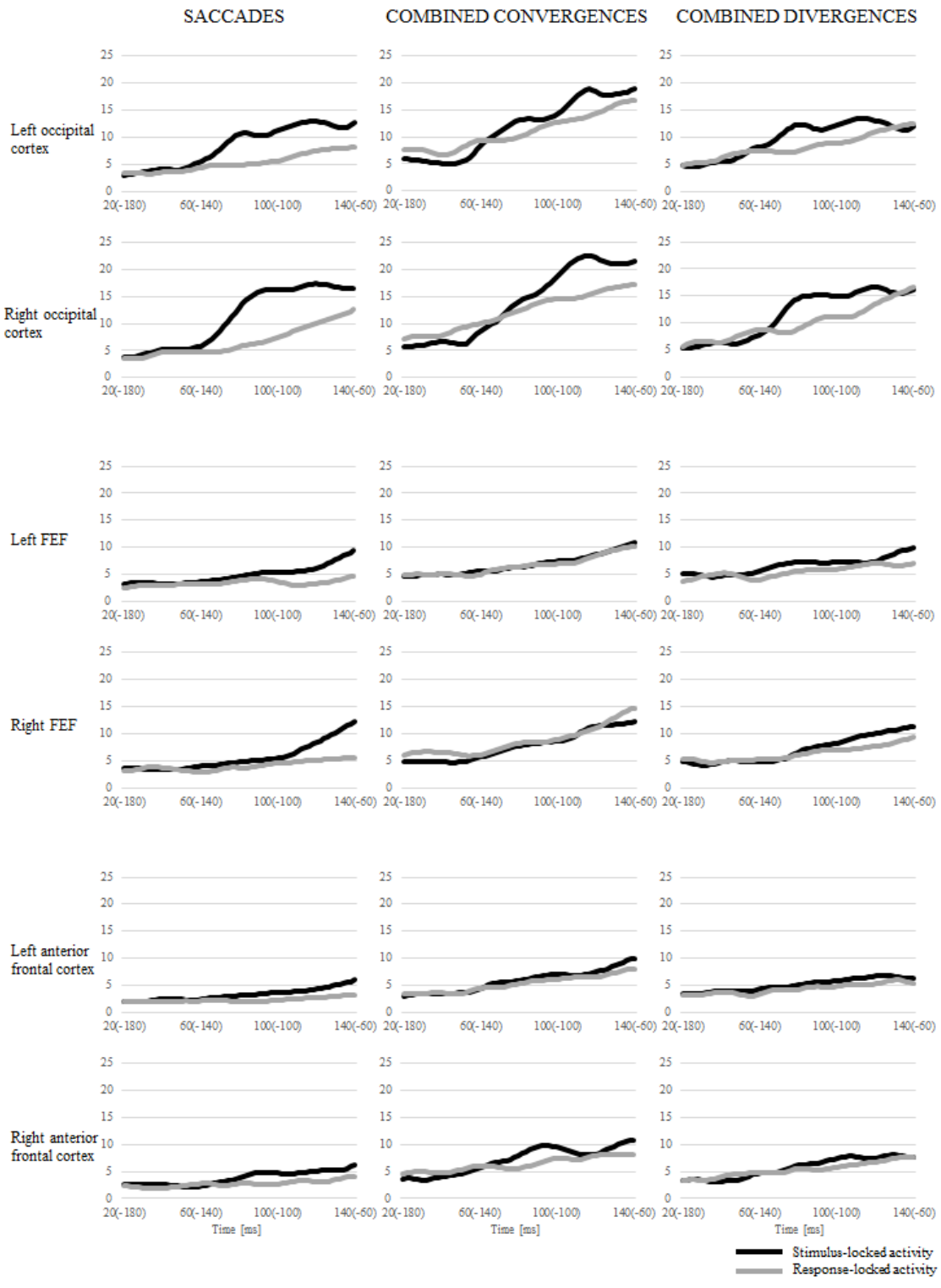

Fig. 20. Source waveforms comparing stimulus-locked and response-locked activities in each regional source for saccades, combined convergences and combined divergences.

Within left and right RS2, a significant preponderance of stimulus-locked activity for saccades was demonstrated (main effect of *event* ($F(5, 65) \geq 53.6$, $p < 0.001$, $\eta^2 \geq 0.8$). Moreover, a significant interaction between *time* and *event* revealed that this

preponderance concerned the time interval from 60 – 140 ms after stimulus onset (-140 - -60 ms before eye movement onset) ($F(5, 65) \geq 8.5$, $p < 0.001$, $\eta^2 \geq 0.39$). For combined divergences also a main effect of *event* was observed ($F(5, 65) \geq 7.9$, $p \leq 0.015$, $\eta^2 \geq 0.38$). The preponderance of the stimulus-locked activity concerned the 60 – 120 ms time interval for left RS2 (*time* * *event*, $F(5, 65) = 5.8$, $p < 0.001$, $\eta^2 = 0.31$) and the 80 – 120 ms time interval for right RS2 (*time* * *event*, $F(5, 65) = 4.2$, $p = 0.011$, $\eta^2 = 0.24$). Within the RS2 we did not observe differences between the stimulus- and response-locked activity for combined convergences (main effect of *event* $F(1, 13) \leq 3.1$, $p \geq 0.1$, $\eta^2 \leq 0.19$), but significant interaction between *time* and *event* for the right RS2 ($F(5, 65) = 6.18$, $p = 0.002$, $\eta^2 = 0.32$) was observed. A post-hoc test revealed that the stimulus-locked activity was higher than the response-locked activity, which concerned the -100 to -80 ms time window (100 – 120 ms after the stimulus onset) ($p = 0.001$).

Within both the right and left RS3, for saccades a higher stimulus-locked than response-locked activity was observed (main effect of *event* $F(1,13) \geq 17$, $p \leq 0.001$, $\eta^2 \geq 0.57$) which concerned the 100 – 140 ms time interval (*time* **event*, $F(5, 65) \geq 9.0$, $p < 0.001$, $\eta^2 \geq 0.41$). For combined divergences a significant main effect of *event* was observed only for the left RS3 and stimulus-locked activity was higher than the response-locked ($F(1, 13) \geq 10.9$, $p = 0.006$, $\eta^2 \geq 0.46$), whereas for the right RS3 the differences between the stimulus-locked and response-locked activities were not significant (main effect of *event* $F(1, 13) = 2.7$, $p = 0.124$, $\eta^2 = 0.17$). However, the significant interaction between *time* and *event* ($F(5, 65) = 3.3$, $p = 0.033$, $\eta^2 = 0.2$) revealed that in the last time window 120 – 140 ms differences between the stimulus-locked and response-locked activity was significant showing a preponderance of a stimulus related activity. For combined convergences no differences between stimulus- and response-locked activities were observed (main effect of *event* $F(1, 13) \leq 1.7$, $p \geq 0.212$, $\eta^2 \leq 0.12$)

Activity was larger within the left and right RS1 stimulus-related activity than the response-related activity for saccades (main effect of *event* $F(1, 13) \geq 34.9$, $p < 0.001$, $\eta^2 \geq 0.73$) and it was related mainly to the 80 – 140 ms time window (*time* * *event*, $F(5, 65) \geq 3.7$, $p \leq 0.071$, $\eta^2 \geq 0.32$). For combined divergences we only observed overall differences between the stimulus- and response-locked activities (main effect of *event* $F(1, 13) \geq 4.9$, $p \leq 0.044$, $\eta^2 \geq 0.28$) with a preponderance of stimulus-related activity. For the left RS1, no significant differences for combined divergences between stimulus-locked and response-locked activities over time were observed (*time* * *event*, $F(5, 65) = 0.6$, $p = 0.686$, $\eta^2 = 0.04$). In turn, for the right RS1 the interaction between *time* and *event*

was significant, ($F(5, 65) = 3.3$, $p = 0.024$, $\eta^2 = 0.2$), however post-hoc tests showed that it did not concern any type of eye movement ($p > 0.1$). No difference between stimulus- and response-locked activity was observed for combined convergences (main effect of *event* $F(1, 13) \leq 4.6, p \geq 0.051, \eta^2 \leq 0.26$). However, we observed a significant interaction between *time* and *event* for the right RS1 ($F(5, 65) = 3.8$, $p = 0.01$, $\eta^2 = 0.23$). The stimulus-locked activity was higher than the response-locked activity and the post-hoc test showed that it was observed in the -120 to -100 ms time window (80 – 100 ms after the stimulus onset) ($p = 0.012$).

Overall, the stimulus-locked activity was larger than the response-locked activity in the case of saccades and combined divergences, especially within RS2 concerning a time interval of about 100 ms after stimulus onset. Within RS1 and RS3 still the overall preponderance of activity related to stimuli was observed for saccades and combined divergences. However, for saccades we observed similar results with the enhanced preponderance of the stimulus-locked activity in 80 – 140 time interval, but for combined divergence there was no difference between stimulus related and response related activities in any time window. For combined convergences no differences between the stimulus- and response-locked activities were observed.

Finally, we compared a contralateral stimulus-locked activity for the three types of eye movement within RS2 (Fig 9). Here we calculated the contralateral activity for saccades, combined convergences and combined divergences (i.e., averaged activity which evoked rightward eye movement within the left RS2 and leftward eye movements within the right RS2). An ANOVA with two factors was performed: *time* (6), and *eye movement type* (3). Comparable activities for all conditions would suggest that activity solely depends on stimulus processing while differences between conditions might support the involvement of additional processes like the detection of crossed or uncrossed disparity. Interestingly, within the occipital cortex a significant main effect of *eye movement type* was observed ($F(2,26) = 8.5$, $p = 0.004$, $\eta^2 = 0.40$) and post-hoc tests revealed that combined convergences were related to higher activity as compared to saccades ($p = 0.002$) and combined divergences ($p = 0.014$) as well. Moreover, the interaction of *time* and *eye movement type* ($F(10,130) = 2.8$, $p = 0.038$, $\eta^2 = 0.18$) and a post-hoc test revealed that the differences between conditions concerned the time windows from 100 ms till 140 ms after stimulus onset ($p < 0.008$).No differences were observed between saccades and combined divergences ($p = 0.64$).

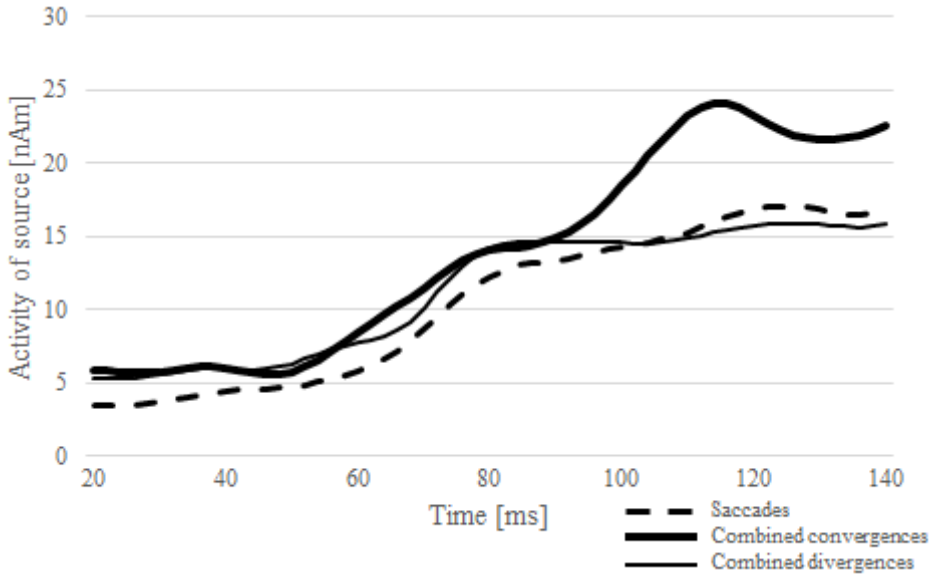

Fig. 21. Contralateral source activity elicited by eye movement preparation in occipital source RS2. Source waveforms were prepared per participant by calculating the RMS (root mean square) for each condition within a regional source. Then, the averages of all individuals per condition and contralateral activity were computed. Finally, the result is shown in the figure. The obtained averages for each type of eye movement were used for statistical analyses.

2.3.5. THE INFLUENCE OF FAR AND NEAR STIMULI FOR CORTICAL ACTIVITY WITHIN OCCIPITAL SOURCE RS2

In the present study, we also asked whether differences between saccades and vergences (mainly combined convergences and divergences) are possibly due to differences in perception between near and far LEDs, e.g. higher illumination of LEDs presented at near, and thus higher stimulation of the retina and or the size of LEDs. To answer this question, we directly compared the stimulus-locked activity within RS2 between saccades performed at both near and far distances as similar activation for both types of saccades ensures that differences between different eye movement types are not due to the illumination of different LEDs. We performed a repeated measures ANOVA with the following factors: *time* (six 20-ms time windows starting from 20 ms to 140 ms relative to stimulus onset), and *distance* (near and far). Here, results indicated that occipital activity was independent of distance (main effect of *distance*, ($F(1,13) < 0.1$, $p = 0.891$, $\eta^2 < 0.01$). We observed a significant interaction between *time* and *distance* ($F(1,13) = 3$, $p = 0.047$, $\eta^2 = 0.17$), however, post-hoc tests revealed that in none of our time windows a difference was observed between near and far saccades ($p > 0.254$).

2.4. DISCUSSION

In the present study, we specifically addressed the question whether the brain areas thought to be relevant for the execution of exogenously triggered eye movements, as identified with the source analysis, are differentially involved depending on the type of eye movement (i.e., saccades, combined convergences, and combined divergences). We also intended to improve our understanding of the observed activities of these brain areas. For example, we would like to know whether the observed activities are more strongly related to eye movement execution, or to specific perceptual processes that are required to perform the different eye movement types.

Saccades were characterized by the shortest latencies, intermediate latencies were observed for combined divergences, while the longest latencies were observed for combined convergences. These results replicate previous findings [161, 190, 191], although some other studies observed the longest latencies for divergences [192, 193]. In general, it can be concluded that vergences are characterized by longer latencies compared to saccades [162]. This seems to imply that the preparation of exogenously triggered combined vergences engage additional processes (e.g., attentional and/or visuomotoric) needed to carry out these eye movements. This could be associated with disparity detection, which differentiates saccades from vergence eye movements. Furthermore, discrepancies in the latencies between the vergence conditions may be related to the detection of different types of binocular disparity (the differences in the location of the stimuli on the retina between the right and left eye). The latency differences seem related to crossed disparity in the case of combined convergences and uncrossed disparity in the case of combined divergences.

The main goal of the present study was to determine and understand the role of different cortical areas for the execution of natural eye movements that involve a depth component. Analyses with BESA on the grand averages on ERPs revealed that three pairs of regional sources may account for the observed ERPs within the -180 -60 ms time interval. Based on Talairach Client software (version 2.4.3), we estimated that these source pairs are located within the occipital cortex, FEF, and an anterior frontal area, which correspond to RS2, RS3, and RS1 respectively. Based on the observed correlations between EOG and the anterior frontal sources, and on the vicinity of the left and right orbits the activity of the anterior frontal source was interpreted as a residual eye movement artifact that was not fully excluded with the ICA procedure.

Our results revealed that significantly the largest response-locked activity was related to the occipital cortex and no differences were observed between both frontal areas. These results may be related to the primary and crucial role of the occipital cortex, associated with the projection to higher-order cortical areas [99, 100], which triggers neuronal circuits engaged in the execution of eye movements. This hypothesis strongly corresponds to the fitting procedure, in which the occipital cortex was fitted to the second and FEF to the third time interval. Altogether, these findings may reflect the temporal sequence of the engagement of the indicated cortical areas. Moreover, regardless of the source location, combined convergences generally induced a larger response-locked activity compared to saccades and combined divergences. Since our results show a general preponderance of stimulus-locked as compared to response-locked activity this suggests that the estimated source activities are related to sensory aspects preceding eye movement execution.

We additionally noticed that irrespective of the direction of the executed eye movement, source activity in the right hemisphere was always larger than in the left hemisphere, and this effect was observed for all regional sources. These observations seem in line with the view that spatial attention especially concerns the right hemisphere as it deals both with left and right external space while the left hemisphere seems only related to right external space [113]. An earlier study with saccades also reported this same asymmetry [114], which was related to spatial attention [114, 194]. Furthermore, our results are also in accordance with studies on hemispatial neglect [195], as problems with spatial attention are often associated with right hemispheric lesions within both occipital and parietal regions.

Although the determination of the engaged cortical sources was one of the major aims of the present study, quite crucial and interesting conclusions may be derived from the comparison of response-locked and stimulus-locked activity source activities. This analysis allows for a more detailed interpretation of the observed source activities. A preponderance of a response-locked activity would suggest that the activity relates to motoric aspects of eye movement generation, whereas the preponderance of stimulus-locked would point to sensory-related processing of the eye movement inducing stimuli. Our results revealed a preponderance of stimulus-related activity for saccades and combined divergences, and no difference between stimulus-related and response-related activities for combined convergences. The overall lack of a preponderance of response-locked activity, but general preponderance of stimulus-locked activity indicates that the

activity of the determined cortical sources is strongly related to stimulus processing. Our results seem to be partially in line with the above-mentioned division indicated for saccades by Schiller et al [119, 180]. They suggest that an anterior stream including FEF is related to target processing, whereas a posterior stream including subcortical areas mediate eye movement execution.

The occipital cortex has obviously a crucial role in the processing of various aspects of visual stimuli [99, 100, 101, 102, 196, 197]. Our results demonstrate that a stimulus-locked activity is in general larger than a response-locked activity, which confirms the view that the engagement of the visual cortex in our study is more related to stimulus processing than to eye movement execution. Interestingly, the preponderance of stimulus-locked activity compared to response-locked was particularly evident at about 100 ms after stimulus presentation which may be associated with the posterior P1 component elicited by visual stimuli [69, 198]. Importantly, our results additionally revealed a greater response of the occipital cortex for combined convergences and combined divergences as compared to saccades. This observation seems to imply that perceptual processing within the occipital cortex depends on eye movement type and is not solely related to the processing of stimulus features. This interpretation is in accordance with the identification of binocular neurons within V2, as already reported by Hubel and Wiesel (1970) [199] and Chen et al. (2008) [200]. Larger activity for combined convergence compared also to combined divergence may reflect the higher number of near cells than far cells within this area, however, according to our knowledge, there is no evidence to support this hypothesis. Alternatively, the increased activity may also be viewed as an attentional modulation of the P1 component (e.g., see Van der Lubbe and Woestenburg, 1997 [71]), which would suggest that more attention is needed for combined convergences than for combined divergences and pure saccades. To sum up, the activity observed within the occipital cortex in our study seems to reflect the further processing of specific stimulus features that crucially depends on the type of eye movement that has to be performed.

For FEF, the largest activity was observed for both vergence conditions. Therefore, we think that this pattern of activity reflects a process related to depth cues, i.e. retinal disparity. The engagement of frontal areas in vergence eye movements was also observed and emphasized by Gamlin and Yoon [167]. They found that near and far response neurons, stimulated by crossed and uncrossed disparity respectively, are present in FEF. Additionally, Ferraina et al. [166] showed that many FEF neurons are sensitive

to retinal disparity. She also suggested that FEF, beyond the detection of retinal disparity, may be engaged in shifting fixation to stimuli in three-dimensions. The observed anatomical connections seem also in line with the idea that FEF is related to vergence eye movements, since connections have been found with areas that are sensitive to retinal disparity, like the primary visual cortex [155], a middle temporal area [201], medial temporal superior area [202] and the nucleus reticularis tegmenti pontis [167] in the brainstem.

As indicated above, we think that the third regional source that we localized in an anterior frontal area, is possibly a residual eye movement artifact. We observed more activity for this source when preparing complex eye movements, which might be related to a kind of tremor generated by the eyes that is triggered by depth cues. Alternatively, this prefrontal activity may reflect the activity of a "compensatory mechanism" that was initially observed in the elderly, as larger involvement of prefrontal cortex was observed in both simple and complex tasks [203], which might enable the maintenance of a high task accuracy. Interestingly, a recent study by Berchicci et al. (2012) revealed that in younger adults (close in age to our participants) increased prefrontal activity was observed in a more challenging task [204], which requires additional cognitive processes. Nevertheless, since there is no report in the literature that relates this area with the preparation and/or execution of reflexive eye movements, this alternative interpretation remains tentative.

One might argue that the possible differences between convergences and divergences in our study are possibly due to small differences between the near and far LEDs. To examine this possibility, we compared stimulus-locked source activities for saccades towards far and near locations. Results showed similar activities for both distances. As a consequence, the observed differences in the source activities between convergences and divergences cannot be ascribed to discrepancies between near and far LEDs.

Finally, we were surprised not to see any engagement of the parietal lobe. The posterior parietal cortex (PPC) is known to take part in the process of reading [205], shifting spatial and temporal attention with regard to saccades [115], and part of PPC - PEF is thought to disengage fixation and trigger reflexive saccades [106]. Although parietal areas are also thought to be important for vergences [108, 109, 168, 206], our results did not identify a source within the parietal lobe. As our model was especially built on combined convergences, this lack of support for a parietal source may imply that

this area is related rather to saccades than to vergences, and it may not have revealed processes that are strongly related to saccades. This issue will have to be explored in future studies.

Interestingly, Berchicci et al. also used the BESA method to model the intracranial sources of cortical potentials related to eye movements [11]. They investigated volitional (self-paced) saccades, which cannot be directly compared with reflexive eye movements. In line with our results, they also observed active sources before eye movement onset that were localized within FEF and occipital areas. However, they also observed activity within the intra-parietal sulcus (IPS) and SEF. The absence of these sources in our study may be due to the short time interval between stimulus onset and the onset of the eye movement that could be used for the analyses, since the self-paced saccade paradigm allows investigating a much longer time interval before eye movement onset (about 2,500 ms).

According to our knowledge, this is the first study using a source analysis on ERPs to specify the cortical areas related to the execution of exogenous saccades, combined divergences and convergences. This approach enabled us to specify the relevant neural correlates of eye movements better than approaches that are solely based on ERPs. Furthermore, it allowed us to describe the involvement of these areas with a high temporal resolution, which provides important information about the interplay and role of these areas. This led us to conclude that the identified cortical areas seem more involved with sensory aspects related to the execution of the different eye movement types and not so much their execution. We hypothesize that motor aspects responsible for final execution of the movement are controlled by subcortical areas.

2.5. SUPPORTING INFORMATION

Table 5.Clinical parameters of optometric examination for heterophoria, positive (base-out) and negative (base in) fusional range, the break and recovery point of near point of convergence. In heterophoria measurement + indicates esophoria, whereas – exophoria. Nose means that no break point was observed or reported by the participant.

Parameter	Subject													
	S1	**S2**	**S3**	**S4**	**S5**	**S6**	**S7**	**S8**	**S9**	**S10**	**S11**	**S12**	**S13**	**S14**
Heterophoria at far (prdptr)	-1	0	0	-1	0	-2	-1	0	0	0	0	0	-1	0
Positive fusional range at far (prdptr)	12	20	20	20	25	21	25	24	14	12	23	14	14	18
Negative fusional range at far (prdptr)	9	12	8	8	9	10	9	8	8	6	9	7	8	8
Heterophoria at near (prdptr)	-1	-2	-6	-2	-2	-6	-4	-1	1	-1	-4	-4	-2	0
Positive fusional range at near (prdptr)	20	25	35	30	35	28	35	30	20	22	25	19	18	30
Negative fusional range at near (prdptr)	16	18	25	14	18	14	16	12	14	14	18	16	14	16
Near point of convergence – break (cm)	1	4	3	1	4	5	4	2	2	4	5	5	6	1
Near point of convergence – recovery (cm)	2	5	5	2	6	7	5	3	4	6	7	6	7	2

3. THE ENGAGEMENT OF CORTICAL AREAS PRECEDING ENDOGENOUS VERGENCE EYE MOVEMENTS AND SACCADES[2]

Abstract

Source analysis on ERPs using EEG were performed to determine the cortical areas related to the preparation and execution of endogenous eye movements: saccades, combined convergences and combined divergences. A device with light emitting diodes (LEDs) was used to present the stimuli which triggered all types of eye movements. Each type of eye movements was examined in a separate experimental block and a color of the central LED indicated in which direction the eye movement had to be made. BESA revealed that two source pairs, located within left and right occipital cortex and within left and right FEF, can account for 96.9% and 99.3% of the observed ERPs obtained for stimulus- and response-locked analysis, respectively. Moreover, we showed that one model sufficiently describes all types of eye movements and also stimulus- and response-locked activity. The largest activity was observed within occipital cortex as compared to FEF in case of stimulus- and response-locked activity. For occipital cortex larger stimulus-locked activity compared to response-locked activity and lack of differences in brain activity between different types of eye movements were found. For FEF also general preponderance of stimulus-locked activity was revealed. Moreover, a preponderance of stimulus-locked activity for combined convergences and combined divergences as compared to saccades was observed. Together, these findings suggest that activity within occipital cortex may reflect the processing of stimulus' simple features, whereas FEF have a role in processing of retinal disparity, which is crucial for the execution of vergences.

[2] The authors confirm their contribution to this chapter as follows: 70% Monika Wojtczak-Kwaśniewska, 15% Anna Przekoracka-Krawczyk, 15% Rob van der Lubbe. Detailed contributions are described in the Author contribution statements in Appendix 1, Appendix 2 and Appendix 3, attached at the end of the dissertation.

3.1. INTRODUCTION

Eye movements may be triggered by exogenous events, like a sudden onset or offset of a stimulus, but they can also be triggered by goals or intentions of the observer. The most commonly performed eye movements are a combination of saccades and vergence eye movements. Saccades and vergence eye movements are crucial for everyday visual exploration since they allow for simultaneous shifting the gaze into different directions and depth. In the present study we investigated whether the processes preceding the execution of volitional eye movements, both combined vergences and saccades, engage the same cortical brain areas to the same degree, by using source analysis performed on ERPs derived from the EEG. Furthermore, we intended to specify the roles of the identified areas, i.e., whether they are more relevant for sensory- or motor-related aspects, by comparing stimulus- and response-locked activity.

The neurophysiological correlates underlying volitional vergence eye movements in humans were previously investigated in a study of Alvarez et al. (2010) [168]. Alvarez at al. (2010) [168] used fMRI to investigate a specific type of volitional eye movements – predictive eye movements. The experimental design of this study allowed participants to anticipate the next target, since stimuli for saccades and vergences were illuminated in a repeatable order in three positions although the precise onset of the next target was unknown. Alvarez at al. (2010) observed that predictive saccades and vergences engage quite similar cortical (FEF, SEF, DLPFC, PEF, cuneus, precuneus) and subcortical areas (anterior and posterior cingulate, and the cerebellum). The only observed difference between predictive vergences and saccades concerned the FEF and SEF. The vergence-related FEF and SEF appeared to be located more anteriorly as compared to the saccade-related regions. These results align with the results of rhesus monkeys reported by Gamlin and Yoon (2000) [167]. They employed microstimulation of a region anterior to the saccade-related region of the FEF and thereby elicited changes in vergence and accommodation. Although the study by Alvarez et al. (2010) indicates that both cortical and subcortical areas are comparably engaged in saccades and vergences, the precise functional roles of these areas are difficult to determine with fMRI due to its low temporal resolution, which is in the order of seconds.

Specifying the functional roles of the aforementioned cortical areas might be possible by performing source analyses on the basis of ERPs. Specifically, the BESA method allows to investigate processes with a short duration related to a specific event

(e.g., stimulus onset or the moment of performing a saccade). If activity is larger when computed stimulus-locked than response-locked, then this activity seems more related to processing the stimulus. An opposite pattern, larger response-locked than stimulus-locked activity, would suggest that the observed activity is more related to specifying the response (e.g., see Van der Lubbe et al., 2006 [27]).

Interestingly, in recent study Berchicci et al. (2012) [11] used the BESA method to determine cortical sources and their activities over time related to different eye movement types. Berchicci et al. (2012) determined cortical sources of response-locked activity. Results revealed that four ERP components were characteristic for self-paced saccades. The possible sources of these components were located within the IPS, SEF and FEF. In the experiment which was presented in previous chapter the BESA method was used to determine cortical brain areas associated with exogenous saccades, combined convergences and combined divergences. It revealed that FEF and occipital cortex were involved. Moreover, based on the comparison of response- and stimulus-locked activity, we argued that these cortical areas are more related to stimulus processing than to specifying motoric aspects of eye movement execution. Furthermore, FEF was more activated before executing vergences, especially convergences, than before executing saccades.

Previous studies have investigated and compared the functional anatomy related to exogenous and endogenous saccades [9, 207, 208]. The fMRI studies by Mort et al. (2003) [9] and Bender et al. (2013) [208] revealed that endogenous saccades in humans were related to larger activity of FEF and IPS as compared to exogenous saccades. However, Reuter et al. (2010) [207] did not observe a difference in brain activity between endogenous and exogenous saccades. However, the experimental design in the study by Reuter et al. (2010) may not have efficiently differentiated between endogenous and exogenous saccades, since both conditions were triggered in similar way, which may explain why no differences in brain activity were observed between endogenous and exogenous saccades.

The engagement of FEF in different types of volitional saccades seems to be evident [124]. However, the role of parietal areas in the preparation and execution of volitional eye movements remains a point of debate. Studies in macaque monkeys [209] and humans [210] revealed that FEF lesions cause deficits in volitional saccades but do not affect the execution of reflexive saccades. In turn, lesion of parietal areas resulted in a delay of exogenous saccades, whereas volitional saccades were intact in humans [107]

and primates as well [211]. These findings suggest that FEF are crucial for volitional saccades. However, the role of parietal areas is not that clear as other studies indicated that parietal cortex is relevant for volitional eye movements [9, 207, 208]. A possible reason for this discrepancy in results may be the strong link between spatial attention and saccade preparation [212]. Thus, the observed parietal activity in the studies of Mort et al. (2003) [9], Bender et al. (2013) [208], Reuter et al. (2010) [207] may be more specific to attentional orienting than to preparing a saccade. Moreover, previous studies [213, 214] indicated that parietal areas are engaged in top-down attentional control. The relationship between the preparation of saccades and attentional orienting was also investigated by Van der Lubbe et al. (2006) [27] who revealed that there is indeed a functional overlap between both processes. Interestingly, in their study response-locked and stimulus-locked activity were compared, and this comparison revealed that activity in FEF was more related with saccade execution, while activity in IPS seemed not related to volitional saccade execution, but rather to attentional orienting.

When studying endogenous eye movements different approaches have been employed. For example, in studies by Van der Lubbe et al. (2000, 2006) [27, 215] and Bender at al. (2013) [208] endogenous eye movements were elicited in two steps, which separates the preparation and execution phases of eye movements. In this approach two stimuli are employed. The first stimulus often indicates the direction of the required eye movement (the directional signal) while the second stimulus indicates when the eye movement has to be carried out (the go signal). In the study by Mort et al. (2003) [9] one stimulus indicated both the direction and the moment of the required eye movement. Although this approach does not allow to distinguish between stimulus processing and movement execution, it reflects the more natural viewing condition, wherein preparatory and executive parts of the movements are integrated. Furthermore, it does not engage an additional process like working memory, which is necessary when directional and go signals are presented separately.

In the present study we further examined which cortical areas are crucial for the preparation and execution of endogenous eye movements: saccades, combined convergences and combined divergences, and whether these areas are differentially engaged depending on the type of eye movement. We especially would like to know whether the FEF play a crucial role in the execution of endogenous vergences, as our previous experiment on exogenous eye movements suggested that FEF are more relevant for vergences than for saccades (see Chapter 2). Furthermore, we wanted to clarify

whether parietal areas play a role for the preparation of endogenous vergences and saccades. Apart from determining the relevant areas, we were especially interested in specifying the roles of these areas by comparing stimulus-locked and response-locked activity. Increased response- vs. stimulus-locked activity suggests that the involved areas are more related to eye movement execution, while increased stimulus- vs. response-locked activity suggests that the involved areas are more related to target processing. As we would like to compare our results with our previous findings (Chapter 2 of the current thesis) with exogenous eye movements, we decided to use one stimulus that indicated both the direction and the moment of the required eye movement, since in the case of exogenous eye movements both stimulus processing and execution happen in parallel. Moreover, each type of eye movement was studied in separate blocks to reduce the processing load for our participants.

3.2. MATERIAL AND METHODS

3.2.1. PARTICIPANTS

Twenty-three volunteers took part in the experiment (15 females and 8 males), who were recruited from the local student population at the Adam Mickiewicz University. The mean age of participants was 23.2 years (SD = 1.5). The participants reported to have no history of neurological and psychiatric disorders. The study was approved by the local ethics committee of the Adam Mickiewicz University and was performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants.

3.2.2. OPTOMETRIC EXAMINATIONS

Before the experiment, an optometric examination was carried out to exclude participants with binocular vision disorders. First, the monocular distance and near visual acuities with corrected refractive errors using Snellen's letter chart were measured. Subsequently, the following parameters of binocular vision were determined: (1) distance and near heterophoria by using the prism cover test, (2) the near point of convergence (NPC) by using the push-up technique, (3) interocular suppression by using the Worth 4-dot test, and (4) stereopsis by using the Stereo Fly Test (Stereo Optical Company). All these tests are described in detail in Scheiman and Wick (2008) [216].

Visual acuity of the right and left eyes was in a normal range (logMAR ≤ 0.00). Far heterophoria ranged from 3 prism diopters of exophoria to ortophoria. Near heterophoria ranged from 6 prism diopters of exophoria to 2 prism diopters of esophoria. The break of NPC was less than 6 cm, whereas the recovery of NPC was less than 8 cm. None of the participants presented suppression and all had a stereo acuity of 40 sec of arc.

3.2.3. TASK AND STIMULI

A device with light emitting diodes (LEDs) was used to present the stimuli (see Fig. 22). LEDs were placed on virtual isovergent circles with a lateral separation of 10˚ at three distances: 25 cm, 40 cm and 1 m from the center of eye rotation (located 2.5 cm from the nasal bridge). This lateral separation produced zero retinal disparity for stimuli that should elicit pure saccades and 12° disparity (both crossed and uncrossed) for stimuli that should elicit convergent and divergent eye movements. The participant's chin and forehead were stabilized to exclude head movements, which might affect eye movement performance. In the experiment, three types of eye movements were elicited: saccades, combined convergences and combined divergences. Each type of eye movement had to be performed 128 times. Overall, each participant was presented with 384 trials, separated in a set of three blocks. Each experimental block was preceded by a demo block and one type of eye movement had to be executed in each experimental block, i.e., saccades, combined divergences, and combined divergences. The order of the experimental blocks was counterbalanced, i.e., each participant performed three blocks in different orders. Blocks were separated by ten-minute breaks. To elicit the endogenous eye movements, we manipulated the color of the central LED (which was initially blue and could turn red or green) as a cue, which indicated whether the eye movement had to be executed to the left (in the case of green) or to the right (in the case of red).

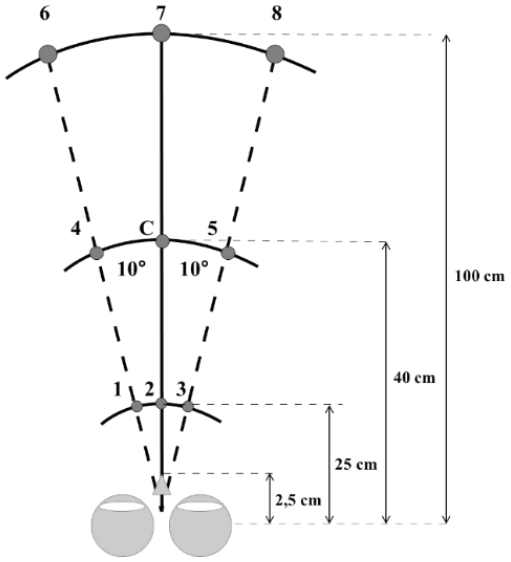

Fig. 22. A graphical representation of the experimental setup. LEDs (light-emitting diodes) were placed at three virtual isovergent circles at three distances 22.5 cm, 37.5 cm and 97.5 cm from the participant's nasal bridge. Each trial started with the onset of the central blue LED (LED C) displayed for a duration that randomly varied between 1000 to 1300 ms. Subsequently, all LEDs were switched on for 700 ms, and then LED C turned green or red and remained on together with all LEDs for 2000 ms. The color of LED indicated in which direction the eye movement had to be made. Each trial ended with a 1000-ms intertrial interval.

Each trial started with the onset of the central LED (LED C in Fig. 22) positioned at 37.5 cm from the nasal bridge, which was presented for a duration that randomly varied between 1000 to 1300 ms in 50 ms steps. Next, all LEDs (1 – 8) were switched on and after 700 ms the central LED turned green or red. Then, all LEDs remained on and after 2000 ms there was an intertrial interval that lasted for 1000 ms. The brightness of LEDs was controlled using a lux meter L-100 (SONOPAN, Białystok, Poland) and was set at the same value for each LED (0.35 lux). The size of the employed LEDs was adjusted to produce the same retinal image. The diameters of the near, middle and far LEDs were 0.3 cm, 0.5 cm and 1.2 cm, respectively.

Before the experiment, the participants received an oral instruction to make an eye movement from the central LED to the target LED as accurately and quickly as possible. Before each experimental block, the participants were informed which type of eye movement had to be performed (i.e., saccades, combined convergences, or combined divergences) and they were also informed that the direction of the required eye movement depended on the color of LED C. Each experimental block was preceded by a demo block

with six trials to ensure that the task was correctly understood. The whole experiment (preparatory and experimental parts) took about three hours.

3.2.4. BEHAVIORAL ANALYSES

Eye movements were recorded by EOG with three bipolar electrodes. Two of them, which were placed on the outer and inner canthi of the left and right eyes, registered horizontal eye movements, and one of them mounted below and above the right eye, registered vertical eye movements and blinks (see Chapter 2). The EOG signal was filtered online with a low-pass filter (30 Hz) and a high-pass filter (0.25 Hz).

The onset of an eye movement was determined with the saccade EOG_{sacc}, which was calculated based on the $hEOG_{left}$ and $hEOG_{right}$ according to the following formula $EOG_{sacc} = (hEOG_{left} + hEOG_{right})/2$. The EMG onset search algorithm (implemented in Brain Vision Analyzer, version 2.0.4) was used to define the onset and peak of each eye movement as follows: the mean amplitude and its standard deviation were calculated for a -100 to 0 ms baseline period. The onset criterion was subsequently set to a quintuple of the SD above or below the mean, depending on its polarity – positive for eye movements performed to the left and negative for eye movements performed to the right. The implemented solution searches for the time point at which EOG_{sacc} activity exceeds 5 SD from the mean of the baseline period. Eye movement latency was defined as a time interval between stimulus onset and eye movement onset. Each trial was additionally visually inspected to exclude improper eye movements from further analyses. This included eye movements performed in the wrong direction (incompatible with the color of the central LED), too slow eye movements (> 450 ms), premature eye movements (< 200 ms) and eye movements preceded or accompanied by blinks. The number of removed trials was 19.1% (SD = 2.8).

3.2.5. EEG RECORDING AND DATA PROCESSING

EEG was recorded from 64 active electrodes located on an ActiCap (Brain Products GmbH) at positions based on the extended International 10-20 system [55]. A ground electrode was placed at the AFz position. The resistance between active electrodes and skin was kept below 5kΩ. An average reference was used, and the signal was amplified by a QuickAmp 128 amplifier (Brain Products GmbH) with a sampling rate of 500 Hz. An online high-pass filter at 0.015 Hz was used.

Data (EEG, EOG and digital markers) was recorded and stored with Brain Vision Recorder software (Brain Products GmbH, version 2.0.3) and subsequently analyzed offline with Brain Vision Analyzer software (Brain Products GmbH, version 2.0.4).

First, data was segmented from -500 to 1500 ms relative to the moment when LED C turned red or green (cue LED onset). The chosen time interval should be long enough to extract the relevant data for the stimulus-locked and response-locked analyses. Trials that did not meet the behavioral criteria (see Behavioral analyses section below) were excluded. Subsequently, an artifact rejection procedure was performed to exclude trials with major artifacts from further analyses (maximum allowed voltage step: 50 μV/ms, minimum/maximum allowed amplitude: ±250 μV, lowest allowed activity difference within 50 ms intervals was 0.1 μV). For artefacts of non-cortical sources, the semiautomatic ICA algorithm was employed. The average number of removed components per participant amounted to 3.6. After the ICA procedure, the artifact rejection procedure was repeated with more strict criteria (maximum allowed voltage step: 50 μV/ms, minimum/maximum allowed amplitude: ±150 μV, lowest allowed activity difference within 50 ms intervals was 0.1 μV). Our artifact rejection procedure implied the removal of 2.5% of the data, which left after the removal of incorrect eye movements. As we were interested in both stimulus- and response-related processes, the data were segmented relative to cue LED onset and eye movement onset, respectively.

3.2.6. SOURCE ANALYSES

BESA software (version 6.0, MEGIS Software GmbH) was used to determine the cortical areas associated with the execution of eye movements. We decided to describe the ERPs registered from 64 electrodes by regional sources (RS), rather than current dipoles, since they allow to create more stable models [86].

The time range during which the location of the regional sources was determined, was based on the eye movement latencies (see Results). As the latencies were rather similar for all eye movement types and ranged from 293 to 314 ms (see Table 5), we choose a time range from 0 to 300 ms for the stimulus-locked analyses and from -300 to 0 ms for the response-locked analyses. A PCA of the grand averages per condition showed that two components can describe 96.9% of the data in stimulus-locked analyses and 99.3 % of data in response-locked analyses. Based on the GFP of the grand averages we determined the relevant time intervals for the source fitting procedure, which were set

from the onset of a peak to the local maximum. Subsequently, for each determined time window the procedure of source fitting was performed. The source model was built on the ERP averaged across all grand averages for each eye movement type (the overall grand average). Inspection of the GFP indicated that two time windows are sufficient for the fitting procedure on stimulus-locked and response-locked data. For the stimulus-locked analyses the following time intervals were chosen: (1) 0 to 104 ms; (2) 118 to 178 ms, whereas for the response-locked analyses, they were selected from: (1)-300 to -242 ms; and (2) -230 to -60 ms. One pair of regional sources was subsequently fit to each time window. Interestingly, the models describing the stimulus- and response-locked data were highly similar.

The fitting procedure resulted in a RV of 1.61% for the stimulus-locked analyses and a RV of 1.64% for the response-locked analyses. Adding additional source pairs did not result in a significant decrease of RV. A model built on the grand averages of stimulus-locked ERPs with an additional third source for the first time interval reduced RV up to 1.21%, whereas this same procedure for the second time interval results in a RV of 0.82%. Similarly, for a model built on the grand averages of response-locked ERPs, RV was reduced up to 1.26% when a third source was added to the first time interval. When a third source pair was added to the second time interval of the response-locked ERPs, no cortical solution was obtained, and RV was reduced up to 0.91%. Based on these results, we preferred to use a solution with two source pairs.

Applying the model based on stimulus-locked activity, response-locked data could be described with a RV of 1.79%, and applying the model based on response-locked activity, stimulus-locked activity could be described with a RV of 1.77%. Based on these results we concluded that one model is sufficient to describe both stimulus- and response-locked activity. Since stimulus-locked activity appeared larger (see Results) than response-locked activity, the model built on the grand averages of stimulus-locked ERPs was considered to be more appropriate for this report. The source model was subsequently used as a filter to estimate changes in activity over time for the identified brain areas, i.e., we applied the model on the ERPs for each eye movement type per participant and then analyzed the source waveforms by computing the root-mean-square (RMS) for each eye movement type and participant [187, 188]. The subsequently obtained data was used for statistical analyses.

3.2.7. STATISTICAL ANALYSES

STATISTICA 12 software was used for the statistical analyses. In all statistical analyses repeated measures ANOVAs were employed. To ensure that observed cortical activity in 20 ms time intervals did not reflect premature eye movements, we examined the 0 to 200 ms time windows for stimulus-locked activity and the -300 to -100 ms time windows for response-locked activity. A significance level of $p < 0.05$ was assumed for all statistical analyses. ANOVAs were followed by post-hoc Tukey tests. Huynh – Feldt ε correction was used when necessary.

3.3. RESULTS

3.3.1. BEHAVIORAL DATA

The latencies of the eye movements were evaluated with a repeated measures ANOVA with two factors: *eye movement type* (saccade, combined convergence, and combined divergence) and *direction* of the eye movement (right or left). The eye movement latencies are shown in Table 5. Statistical analyses revealed a significant main effect of *eye movement type* ($F(2,44) = 4.3$, $p = 0.023$, $\eta_p^2 = 0.16$). Post-hoc tests revealed that differences only concerned latencies of saccades and combined convergences ($p = 0.016$). No differences were observed between saccades and combined divergences ($p = 0.177$) and between both combined eye movements ($p = 0.528$). Although the interaction between *eye movement type* and *direction* was just significant ($F(2,44) = 3.24$, $p = 0.049$, $\eta_p^2 = 0.13$), post-hoc tests revealed no differences between left and right saccades ($p > 0.99$), no difference between left and right combined convergences ($p = 0.99$), and only a trend to a difference between left and right combined divergences ($p = 0.067$). Finally, no main effect of *direction* was observed ($F(1,22) = 0.9$, $p = 0.364$, $\eta_p^2 = 0.04$).

Table 6. Mean latencies for endogenously triggered eye movements: saccades, divergences and convergences. SE represents the standard error.

Eye movement type		Latency [ms]	SE [ms]
Saccades	Right	314	11
	Left	313	11
Divergences	Right	307	11
	Left	296	12
Convergences	Right	293	13
	Left	296	14

Although statistical analysis revealed a significant interaction between *eye movement type* and *direction* differences, the graphical representation of grand averages of EOG for different types of eye movements in Fig. 23 indicates that these differences are negligible.

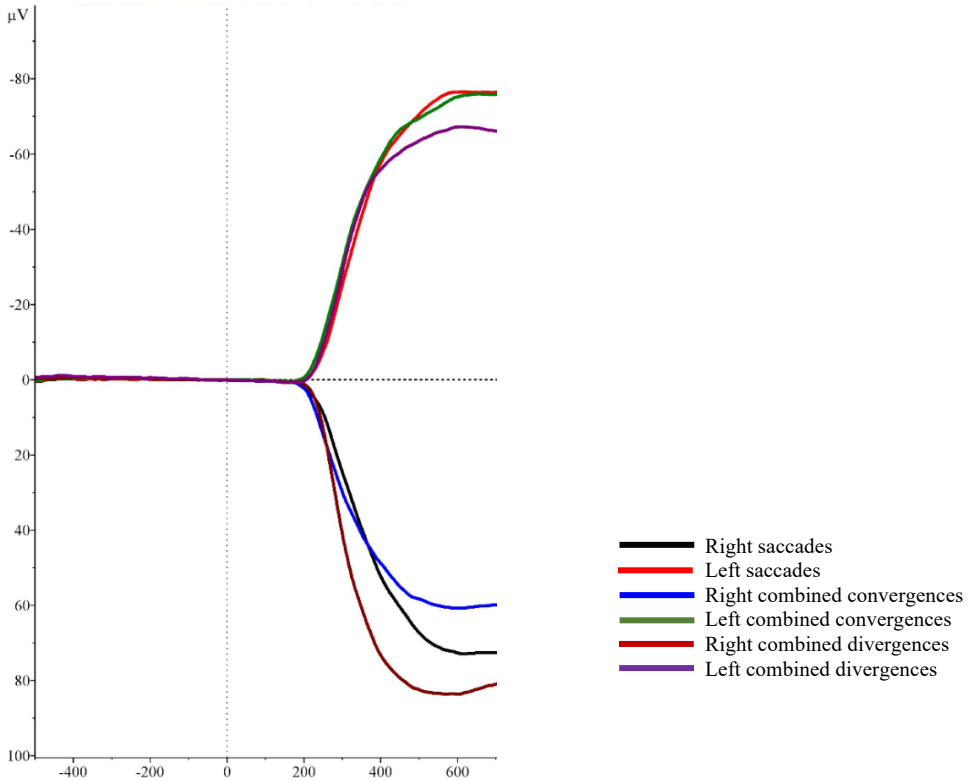

Fig. 23. Grand averages of EOG presented for the following eye movements: left saccades, right saccades, left combined convergences, right combined convergences, left combined divergences and right combined divergences.

3.3.2. EVENT RELATED POTENTIALS

In Fig. 24 and 25 ERPs and the topographical maps of the grand averages related to the stimulus-locked activity are presented. These data were used to prepare the source model that enables a more straightforward interpretation than the comparison of the ERP topographies.

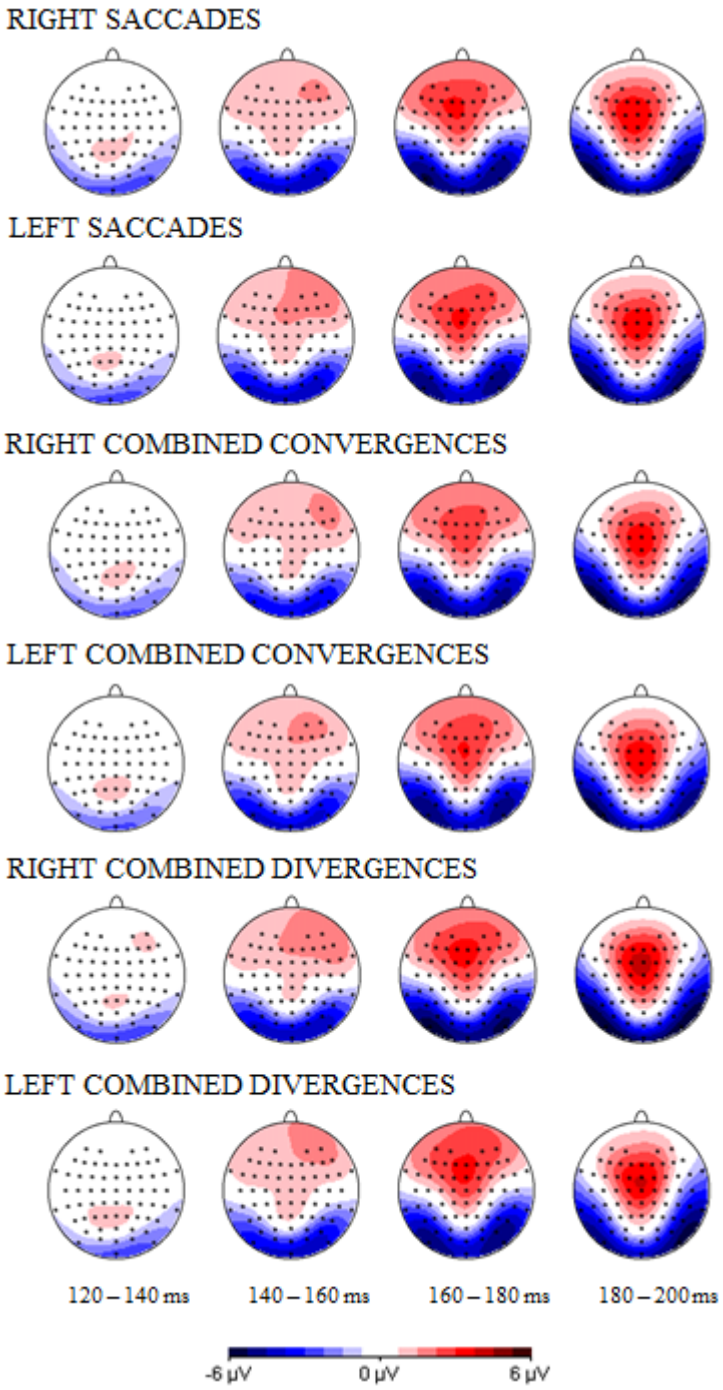

Fig. 24. Topographical maps of event-related potentials (ERPs) for the three eye movement types. Since in the initial time intervals, i.e. 0 – 120 ms, no significant activity was observed, the ERPs from 120 ms to 200 ms relative to the stimulus onset (stimulus-locked activity) was shown.

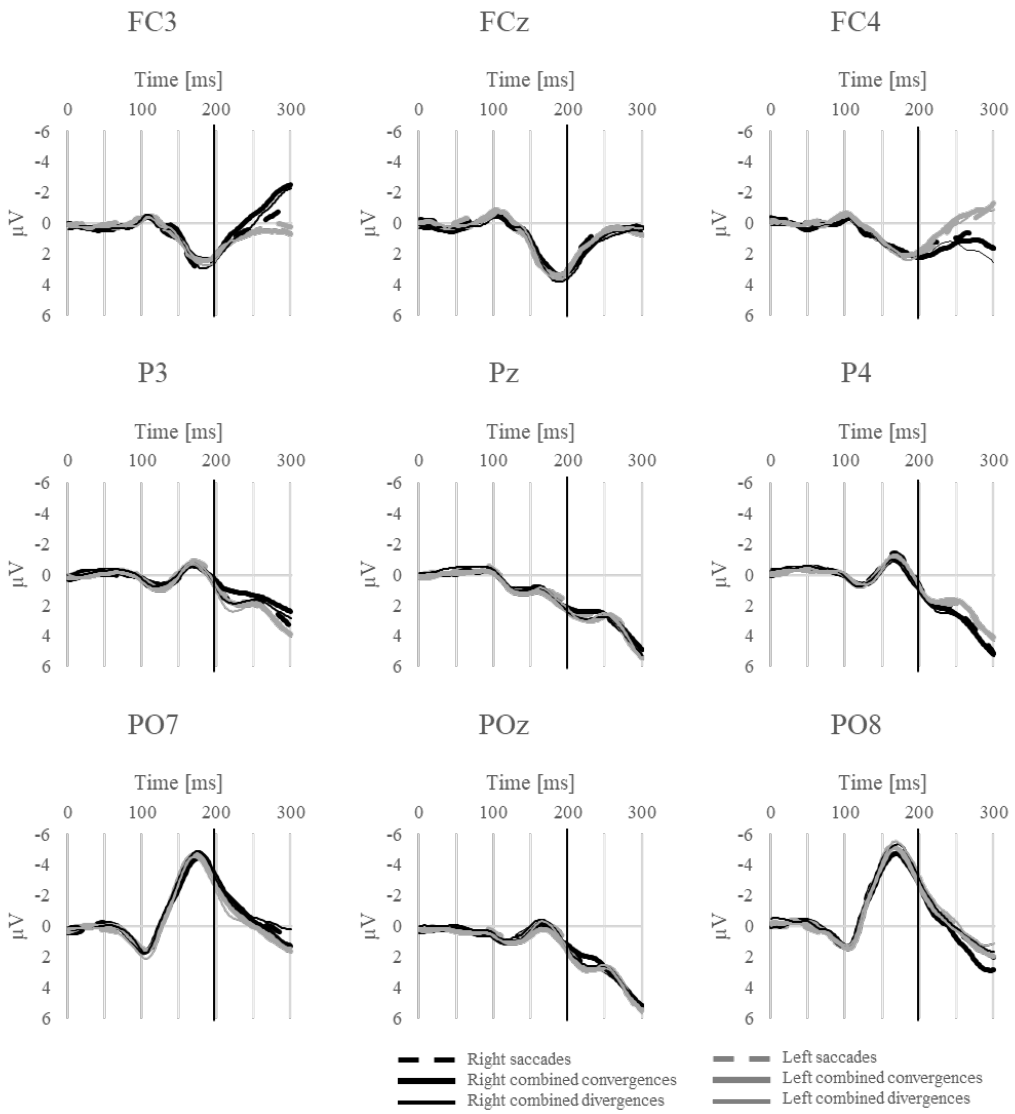

Fig. 25. Grand average waveforms of event related potentials (ERPs) for stimulus-locked activity for the three eye movement types in time intervals from 0 ms to 300 ms relative to the stimulus onset. The grand averages waveforms of the stimulus-locked activity are presented for 9 relevant electrodes located in the frontal, parietal, and parieto-occipital cortex. Black vertical lines represent analyzed time interval, i.e. 0 – 200 ms.

3.3.3. SOURCE ACTIVITIES

Based on the Talairach-Tournoux coordinates determined by BESA and Talairach Client software (version 2.4.3) using Single Point Search [189], the location of the fitted RSs was determined. Source analyses indicated that the RS are localized in FEF and the occipital cortex on the basis of the stimulus-locked analysis and in the inferior frontal gyrus and the occipital cortex on the basis of the response-locked analysis. The precise locations of RSs for both models including both Brodmann areas and Talairach-Tournoux

coordinates are indicated in Table 6. For further analyses, the model based on stimulus-locked activity was chosen (see Method section).

Table 7. Talairach coordinates of regional sources which represent the preparation of three types of eye movements: saccades, combined convergences and combined divergences. A model was built using BESA based on overall grand average of ERP obtained for three types of eye movements for stimulus-locked and response-locked activity. Cortical regions were determined by using the Talairach Client software (version 2.4.3).

	Regional sources	Fitting time intervals	Cortical region	Brodmann Area	X	Y	Z
Stimulus-locked activity	**RS1**	0 to 104 ms	Frontal eye fields	6	+/- 45	-7	34
	RS2	118 to 178 ms	Occipital cortex	17	+/- 24	-71	8
Response-locked activity	**RS1**	-300 to -242 ms	Inferior frontal gyrus	9	+/- 42	-5	24
	RS2	-230 to -60 ms	Occipital cortex	17	+/- 22	-75	5

In Fig. 26, a model displaying the locations of the two regional source pairs is presented.

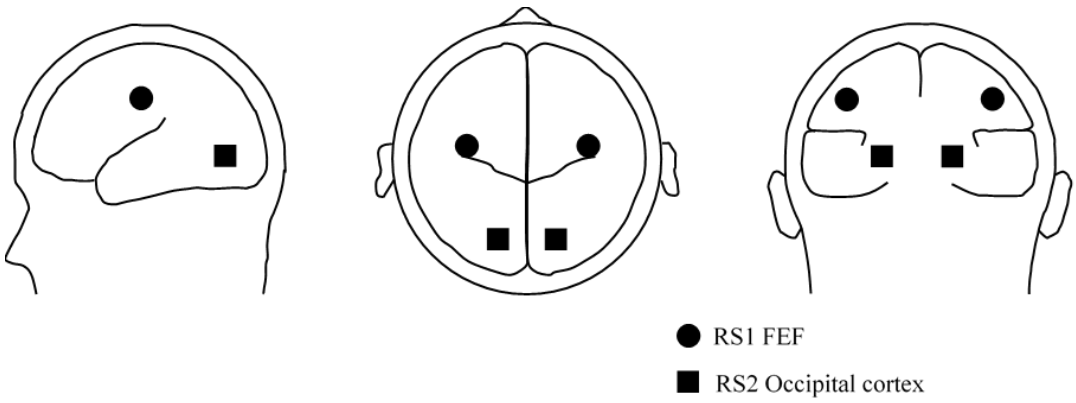

Fig. 26. The location of the estimated pairs of regional sources that describe event-related potentials (ERPs) preceding eye movement execution. A model was built with the BESA method based on the overall grand average stimulus-locked ERPs across all eye movement types. The fitting procedure was performed for two time windows based on inspection of the global field power (GFP). The first regional source (RS1) was fit to a 0 – 104 ms time window, whereas the second source (RS2) was fit to a 118 – 178 ms time window. The chosen model described stimulus-locked data with a RV of 1.61% and response-locked data with a RV of 1.79%.

3.3.3.1. STIMULUS-LOCKED ACTIVITY

Statistical analyses of stimulus-locked estimated source activities were performed using repeated measures ANOVA with the following factors: *source* (RS1, RS2), *time* (ten 20-ms time windows from 0 ms to 200 ms relative to the stimulus onset), *eye movement type* (saccade, combined convergence and combined divergence), *direction* (right or left), and *hemisphere* (right or left). To facilitate the interpretation of complex interactions, ANOVAs were also carried out for each regional source pair separately.

In Fig. 27, source waveforms are displayed that represent stimulus-locked activity preceding eye movement execution for each regional source.

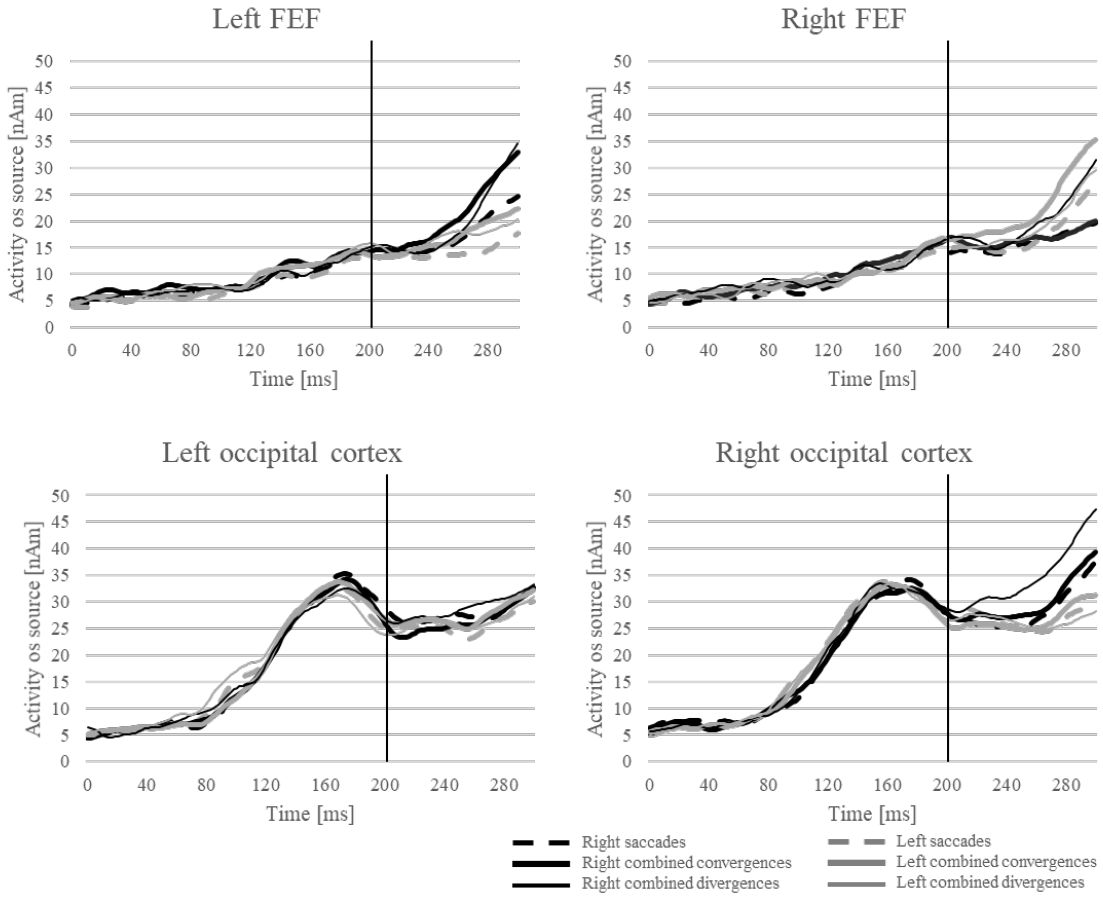

Fig. 27. Source waveforms which represent stimulus-locked activity preceding eye movement execution for each regional source. Source waveforms were obtained by calculating the root mean square (RMS) for each condition within each regional source. Finally, the averages of all participants per each condition were calculated and used for statistical analyses. Black vertical lines represent analyzed time interval, i.e. 0 – 200 ms.

3.3.3.1.1. FRONTAL EYE FIELD (RS1)

For RS1, a main effect of *time* was observed ($F(11,242) = 50.7$, $p < 0.001$, $\eta_p^2 = 0.7$). Contrast analyses showed a linear trend, indicating that observed activity increased over time ($F(1,22) = 104.8$, $p < 0.001$)). Moreover, a main effect of *eye movement type* was also observed ($F(2,44) = 5.6$, $p = 0.007$, $\eta_p^2 = 0.2$; see also Fig. 28). Saccades were characterized by lower activity compared to combined convergences ($p = 0.013$) and combined divergences ($p = 0.021$). No difference in activity was observed between combined convergences and combined divergences ($p = 0.98$).

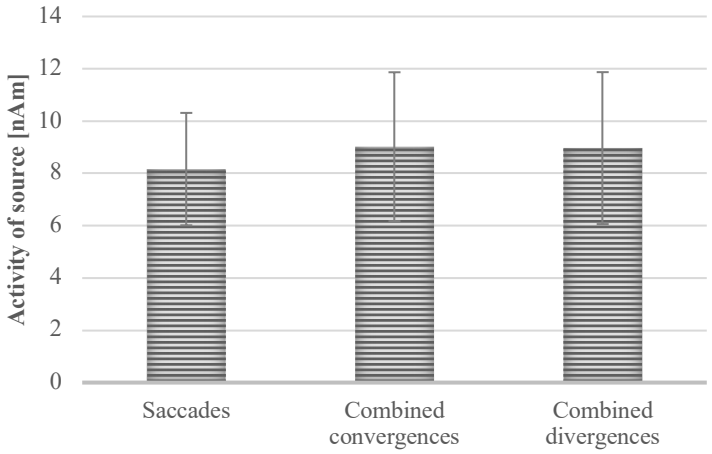

Fig. 28. Graphical representation of differences in stimulus-locked source activity observed for saccades, combined convergences and combined divergences within FEF. Vertical lines represent standard errors.

Statistical analyses revealed that main effects of *direction* ($F(1,22) = 0.1$, $p = 0.729$, $\eta_p^2 = 0.01$) and *hemisphere* ($F(1,22) = 2.5$, $p = 0.129$, $\eta_p^2 = 0.1$) were insignificant. Also interactions between eye movement type, direction and hemisphere were insignificant (*eye movement type* * *direction* interaction $F(2,44) = 0.7$, $p = 0.513$, $\eta_p^2 = 0.03$), *eye movement type* * *hemisphere* interaction $F(2,44) = 0.1$, $p = 0.854$, $\eta_p^2 = 0.01$), *direction* * *hemisphere* interaction $F(1,22) = 0.3$, $p = 0.586$, $\eta_p^2 = 0.01$).

3.3.3.1.2. OCCIPITAL CORTEX (RS2)

For RS2, a main effect of *time* was observed ($F(9,198) = 65.8$, $p < 0.001$, $\eta_p^2 = 0.75$). Activity increased over time, which was confirmed by contrast analyses that showed a linear trend ($F(1,22) = 128.6$, $p < 0.001$). We did not observe differences between eye movement types ($F(2,44) = 0.3$, $p = 0.714$, $\eta_p^2 = 0.02$), direction of the movement ($F(1,22) = 0.6$, $p = 0.451$, $\eta_p^2 = 0.03$), and hemisphere ($F(1,22) = 0.7$, $p =$

0.422, $\eta_p^2 = 0.03$). Interactions between these factors were statistically insignificant (*eye movement type* * *direction*: $F(2,44) = 0.2$, $p = 0.836$, $\eta_p^2 = 0.01$), *eye movement type* * *hemisphere*: $F(2,44) = 0.1$, $p = 0.904$, $\eta_p^2 < 0.01$, *direction* * *hemisphere*: $F(1,22) = 0.3$, $p = 0.625$, $\eta_p^2 = 0.01$).

Only one interaction was significant: the interaction between *time*, *eye movement type* and *hemisphere* ($F(18,396) = 2.4$, $p = 0.022$, $\eta_p^2 = 0.1$). To facilitate the interpretation of these interactions, ANOVAs were performed per time window. The interaction between movement type and hemisphere was significant only in 80 – 100 ms time window ($F(2,44) = 5.9$, $p = 0.008$, $\eta_p^2 = 0.21$). Post-hoc analyses revealed that this difference was related to left hemisphere, where larger activity was observed for combined divergences compared to combined convergences ($p < 0.001$).

3.3.3.2. RESPONSE-LOCKED ACTIVITY

Statistical analyses of response-locked estimated source activities were performed using repeated measures ANOVA with the following factors: *source* (RS1, RS2), *time* (ten 20-ms time windows from -300 ms to -100 ms relative to the eye movement onset), *eye movement type* (saccades, combined convergences and combined divergences), *direction* (right or to left eye movements), and *hemisphere* (right or left). Similarly to the stimulus-locked analysis, ANOVAs were also performed for each regional source separately. Source waveforms of response-locked activity preceding eye movement execution within each regional source are shown in Fig. 29.

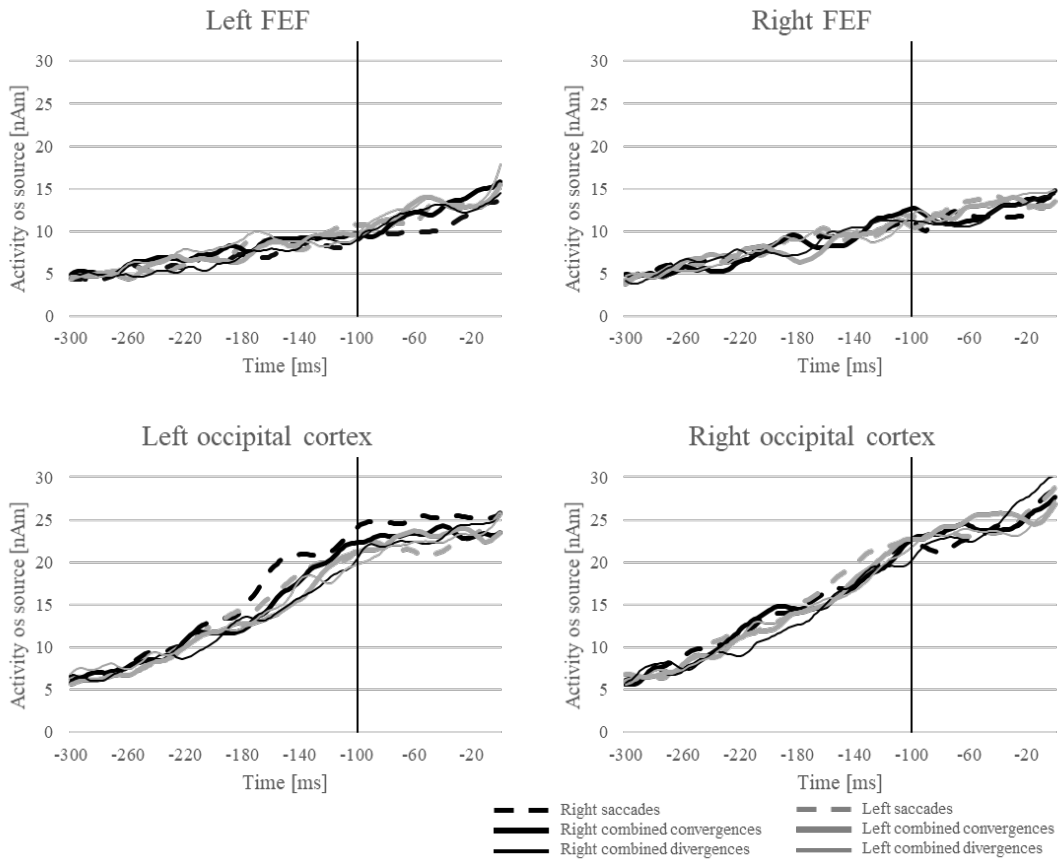

Fig. 29. Source waveforms which represent response-locked activity preceding the eye movement execution for each regional source. Source waveforms were obtained by calculating root mean square (RMS) for each condition within each regional source. Finally, the averages of all participants per each condition were calculated and used for statistical analyses. Black vertical lines represent analyzed time interval, i.e. -300 to -100 ms.

Response-locked analyses also revealed that more activity was present in the occipital cortex than in the FEF (main effect of *source*, $F(1,22) = 50.8$, $p < 0.001$, $\eta_p^2 = 0.7$). Moreover, also interaction between *source* and *time* was significant ($F(9,198) = 26$, $p < 0.001$, $\eta_p^2 = 0.54$). Subsequently, post-hoc tests showed that larger activity observed for occipital cortex compared to FEF was related to the time interval from -260 ms to -100 ms before the eye movement onset ($p \geq 0.036$).

3.3.3.2.1. FRONTAL EYE FIELD (RS1)

A separate analysis for RS1 revealed a significant main effect of *time* $F(9,198) = 46.3$, $p < 0.001$, $\eta_p^2 = 0.68$). A contrast analysis showed a linear trend ($F(1,22) = 74$, $p < 0.001$), which reflected an increase in source activity (see Fig. 29). Analysis of the source activities for RS1 revealed no significant main effects of *eye movement type* ($F(2,44) <$

0.1, p = 0.972, $\eta_p 2$ < 0.01) and *direction* (F(1,22) < 0.1, p = 0.944, η_p^2 < 0.01). Also following interactions were insignificant: *eye movement type* * *direction* (F(2,44) = 1, p = 0.361, η_p^2 = 0.04), *eye movement type* * *hemisphere* (F(2,44) = 0.2, p = 0.793, η_p^2 = 0.01), *direction* * *hemisphere* (F(1,22) = 0.1, p = 0.833, η_p^2 < 0.01).

Only the main effect of *hemisphere* was significant (F(1,22) = 4.5, p = 0.047, η_p^2 = 0.17), which revealed that larger activity was observed for right hemisphere compared to the left hemisphere. The significant interaction between *time* and *hemisphere* (F(9,198) = 2.6, p = 0.038, η_p^2 = 0.11) suggested that this preponderance of right hemisphere was observed in specific time intervals. Post-hoc test showed that it was related to -120 to -100 ms time interval (p < 0.001).

3.3.3.2.2. OCCIPITAL CORTEX (RS2)

For RS2, only the main effect of *time* was statistically significant (F(9,198) = 59, p < 0.001, η_p^2 = 0.73). Contrast analyses showed a linear trend what suggests that the activity increases over time (F(1,22) = 78.2, p < 0.001) (see Fig. 29). Statistical analyses revealed that main effects of *eye movement type* (F(2,44) = 1.9, p = 0.158, η_p^2 = 0.08), *direction* (F(1,22) = 0.1, p = 0.816, η_p^2 < 0.01), *hemisphere* (F(1,22) = 0.5, p = 0.48, η_p^2 = 0.02) were statistically insignificant. Also interactions between these conditions: *eye movement type* * *direction* (F(2,44) = 0.6, p = 0.567, η_p^2 = 0.03), *eye movement type* * *hemisphere* (F(2,44) = 0.4, p = 0.659, η_p^2 = 0.02), *direction* * *hemisphere* (F(1,22) = 1.1, p = 0.302, η_p^2 = 0.05) were insignificant.

We observed one significant interaction between *time* and *eye movement type* (F(18,396) = 2.1, p = 0.029, η_p^2 = 0.09). Performed post-hoc test showed that saccades evoked larger activity compared to combined convergences in -160 to -140 ms time interval (p = 0.012), and compared to combined divergences in -160 – 100 ms time interval ($p \leq 0.044$).

3.3.3.3. A COMPARISON OF STIMULUS- AND RESPONSE-LOCKED ACTIVITY

In the present study we also compared stimulus-locked and response-locked activity to improve our understanding of the observed source activities. We compared obtained activities in overlapping time intervals, i.e. 0 – 200 ms time interval for stimulus-locked activity and -300 to -100 ms for response-locked activity. Thus, we compared the activities in the corresponding time windows 0 – 20 ms with -300 - -280 ms, etc. A

comparison of the response- and stimulus-locked activity for saccades, combined convergences and combined divergences (averaged across left and right movements) for each regional source is presented in Fig. 30. Statistical analyses comparing stimulus- and response-locked activity were performed separately for left and right regional sources, using repeated measures ANOVA with the following factors: *time* (ten 20-ms time windows from -300 ms to -100 ms relative to the eye movement onset for response-locked activity and 0 – 200 ms for stimulus-locked activity), *event* (stimulus- or response-locked activity), *eye movement type* (saccades, combined convergence and combined divergence).

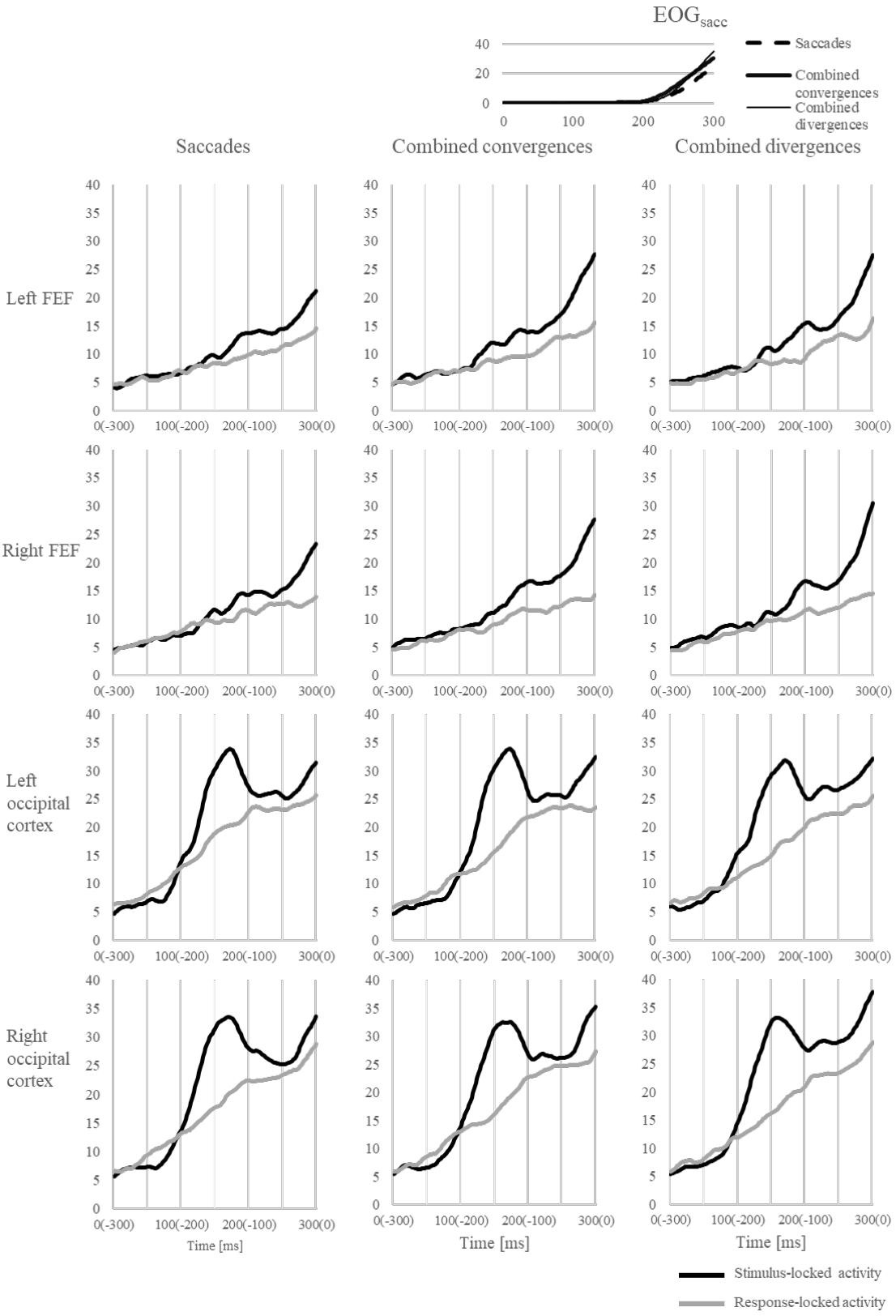

Fig. 30. Source waveforms of stimulus- and response-locked activity obtained for saccades, combined convergences and combined divergences in each regional source.

For left FEF a significant main effect of *event* was observed ($F(1,22) = 9.2$, $p = 0.006$, $\eta_p^2 = 0.29$). Here, also a general preponderance of stimulus-locked activity was revealed. The significant interaction between *time* and *event* ($F(9,198) = 9.2$, $p < 0.001$, $\eta_p^2 = 0.37$) revealed that the preponderance of stimulus-locked activity was observed in 140 – 200 ms time interval (-160 to -100 ms time interval before the eye movement onset) ($p < 0.001$) . Interaction between *event* and *eye movement type* was also significant ($F(2,44) = 3.3$, $p = 0.047$, $\eta_p^2 = 0.13$) showing that this preponderance of stimulus-locked compared to response-locked activity was observed for combined convergences ($p < 0.001$) and combined divergences ($p < 0.001$). No differences were observed for saccades ($p = 0.063$).

Interestingly, for right FEF, a significant main effect of *event* was observed ($F(1,22) = 7.6$, $p = 0.011$, $\eta_p^2 = 0.26$). A general preponderance of stimulus-locked activity was revealed. Also significant interaction between *time* and *event* was observed ($F(9,198) = 6.8$, $p < 0.001$, $\eta_p^2 = 0.24$). Performed post-hoc test revealed that stimulus-locked activity was larger compared to response-locked activity in 160 – 200 ms time interval (-140 to -100 ms time interval before the eye movement onset) ($p < 0.001$). Moreover, a significant interaction between *event* and *eye movement type* ($F(2,44) = 3.9$, $p = 0.035$, $\eta_p^2 = 0.15$) showed that preponderance of stimulus-locked activity concerned combined convergences ($p < 0.001$) and combined divergences ($p < 0.001$). No differences were observed for saccades ($p = 0.36$).

For left occipital cortex also a significant main effect of *event* and general preponderance of stimulus-locked activity was observed ($F(1,22) = 17.1$, $p < 0.001$, $\eta_p^2 = 0.44$). Also interaction between *time* and *event* was statistically significant ($F(9,198) = 24.1$, $p < 0.001$, $\eta_p^2 = 0.52$). Post-hoc test revealed that preponderance of stimulus-locked activity was observed in 120 – 200 ms time interval (-180 to -100 ms time interval before the eye movement onset) ($p < 0.001$). Significant interaction between *time, event* and *eye movement type* ($F(18,396) = 2.3$, $p = 0.008$, $\eta_p^2 = 0.09$) showed that the preponderance of the stimulus-locked activity for each eye movement type was dependent on time. For saccades it was observed from 120 to 200 ms (-180 to -100 ms before eye movement onset) ($p < 0.001$), for combined convergences from 100 to 200 ms (-200 to -100 ms before eye movement onset) ($p < 0.009$), whereas for combined divergences from 80 to 200 ms (-220 to -100 ms before eye movement onset) ($p < 0.022$).

For the right occipital cortex a significant main effect of *event* was observed ($F(1,22) = 24.8$, $p < 0.001$, $\eta_p^2 = 0.76$). Stimulus-locked activity was larger than response

locked activity. Also significant interaction between *time* and *event* was observed ($F(9,198) = 19.3$, $p < 0.001$, $\eta_p^2 = 0.47$). Post-hoc test showed that larger activity for stimulus-locked activity was observed in 120 – 200 ms time interval (-180 to -100 ms time interval before the eye movement onset) ($p < 0.001$). However, this preponderance of stimulus-locked activity was not dependent on *eye movement type* since the interaction between *event* and *eye movement type* was not significant ($F(2,44) = 1.8$, $p = 0.179$, $\eta_p^2 = 0.08$).

3.4. DISCUSSION

In the present study we examined which cortical areas have a relevant role in the preparation and execution of endogenous vergences and saccades. As the outcomes of previous studies are inconsistent in determining the relevant brain areas related to endogenous eye movements, we specifically would like to know whether FEF and parietal cortex are crucial for the execution of this type of eye movements. Moreover, as the results of our previous study presented in Chapter 2 suggested that FEF have a relevant role in exogenous vergences, we also wanted to know whether a similar pattern of activity, i.e., larger activity of FEF for vergences as compared to saccades, can be observed in the case of endogenous eye movements. Finally, we also would like to know whether this cortical activity reflects sensory or rather motor aspects of eye movement execution, thereby improving our understanding of the roles of the identified areas in endogenously triggered eye movements.

First, we will discuss and interpret the observed source activities to specify the various roles of the identified brain areas related to the execution of the different eye movements. Secondly, we will focus on the questions mentioned above: we will discuss the role of FEF and parietal cortex in endogenous eye movements. To improve our understanding of the role of cortical areas in the execution of endogenous eye movements, we will also focus on the implications of the observed differences between response-locked and stimulus-locked activity. Finally, we will shortly discuss the behavioral results, since they may give relevant information related to the complexity of the processes that preceded the execution of eye movements.

Application of the BESA method on the overall grand average ERPs showed that two pairs of regional sources can account for the observed ERPs (RV = 1.61% for the stimulus-locked analyses and RV = 1.79% for response-locked activity). Application of

Talairach Client software (version 2.4.3) indicates that the identified regional sources are located within left and right occipital cortex and within left and right FEF. One model could sufficiently describe all different eye movement types, in line with Alvarez et al. (2010) [168], who revealed that volitional saccades and vergences engage similar brain areas and with findings presented in previous chapter.

Our results revealed that largest activity was observed within occipital cortex as compared to FEF both in the case of stimulus- and response-locked analyses. This activity was also larger in the case of stimulus-locked than in the case of response-locked analyses. This stimulus-locked preponderance may reflect the primary role of occipital areas in their projection to higher-order cortical areas [99, 217]. Moreover, this activity within occipital cortex was the same for different eye movement types, both in the case of stimulus- and response-locked analyses. This lack of a difference may highlight the role of occipital cortex in processing features of presented stimuli [99, 101, 102, 196], rather than processing those aspects that are characteristic for each type of eye movements (e.g., crossed disparity for combined convergences or uncrossed disparity for combined divergences). Interestingly, a peak in stimulus-locked activity was observed at about 150 – 180 ms after the stimulus that triggered the eye movements. In previous experiment, which investigated exogenously triggered eye movement, we did observe the overall increase of stimulus-locked activity, however we did not observe such clear peak as in the present study. Based on previous results [74] we hypothesized that this peak reflects the involvement of working memory as in our study the meaning of the central LED color had to be remembered, as it cued the direction of the following eye movement. The peak may also be related to the P2 component, which was suggested to be generated in parieto-occipital regions [73], what is in line with the presented results.

For FEF, for stimulus-locked activity a preponderance of activity for combined convergences and combined divergences as compared to saccades was observed. No differences were found between both vergence conditions. Based on these results, we may hypothesize that part of this activity is specific for vergences. This may be related to the processing of retinal disparity, which is crucial for properly executing vergences. The idea that FEF plays a special role for vergences fits with studies that revealed a connection between FEF and the nucleus reticularis tegmenti pontis in the brain stem, which is sensitive to retinal disparity [218]. This also corresponds with the results of Gamlin and Yoon (2000) [167] reported in the introduction. They revealed the presence of near and far neurons within FEF, which respond to crossed and uncrossed disparity, respectively.

Additionally, the study by Ferraina et al. (2000) [166] on exogenous vergences also revealed the presence of disparity sensitive neurons within FEF. Finally, in previous study on exogenous vergences and saccades presented in Chapter 2, it was observed that FEF is more active for exogenous vergences than for saccades.

As far as we know, the results of one study with endogenous saccades suggested that FEF is rather related to saccade triggering, as a positive anterior lateralized component was observed shortly before saccade onset [27]. Possibly, this difference in observations is due to slight procedural differences. In the current study, we used one stimulus that specified both the direction and the moment of executing the eye movement, while in the study of Van der Lubbe et al. (2006) [27] saccades were elicited in two steps. Possibly, the mixture of processing the direction and triggering the eye movement in the current study has masked this response-related activity.

Another question that we wanted to address concerned the role of parietal cortex for the preparation and execution of endogenous eye movements. Interestingly, no parietal source was identified in our study. Previous studies indicated that parietal cortex has a crucial role in disengagement of fixation and in triggering exogenous saccades [106, 110, 219]. However, parietal cortex is known to be involved with spatial attention related to reflexive saccades [115]. Thus, no strong support is available that parietal cortex plays a crucial role in the execution of endogenous saccades and vergences.

Interestingly, we observed no major latency differences between saccades and vergences. Previous studies showed that vergences are characterized by the longest latencies [161, 162, 190], but these studies focused on exogenous eye movements. The similar latencies obtained in our study may be related to the employed experimental design, since the three eye movement types were investigated in separate blocks. As a consequence, the only unpredictable aspect for the participants was the direction of the required eye movement, which may have resulted in similar latencies.

In conclusion, the present study provides novel information on the activity of cortical sources preceding endogenous saccades and vergences. Our study revealed that two source pairs can describe the observed ERPs – one located in FEF and one located in occipital cortex. The preponderance of stimulus-locked activity suggests that both cortical areas are related to sensory aspects of the eye movements. Activity observed in occipital cortex may reflect the processing of stimulus' simple features, whereas activity in FEF may be more related to retinal disparity and vergences.

4. GENERAL DISCUSSION

Combined vergences, which require simultaneous redirection of gaze into different directions and depths, are probably the most common type of eye movements, which are performed to explore the surrounding environment. Although combined vergences are highly relevant for 3D perception, research on this type of eye movements is rare and therefore the neural control of combined vergences is not very clear. Moreover, previous studies that investigated the functional anatomy related to vergences used mostly fMRI or ERP techniques. Although fMRI provides high spatial resolution, it does not allow to determine the precise role of the active brain areas due to low temporal resolution. ERPs, in turn, which can be derived from EEG, are characterized by a high temporal resolution, nevertheless the interpretation of ERP topographies does not enable clear conclusions. It seems that the BESA method used in the experiments presented in this thesis solves the problems related to limitations of both approaches. BESA allows to determine the likely involved cortical sources and, as it is based on ERP, also provides high temporal resolution, which enables the comparison of stimulus- and response-locked activities. Larger stimulus-locked activity compared to response-locked activity suggests the involvement of estimated sources in specific brain areas related to target processing, whereas larger response-locked activity compared to stimulus-locked activity implies their involvement in processes related to eye movement execution. Thus, BESA enables a more straightforward interpretation of the outcomes. According to our knowledge, these are the first studies that used the BESA approach to investigate cortical correlates related to the preparation and execution of exogenous and endogenous combined vergences and saccades. The outcomes of the presented experiments will likely increase our understanding of the neurophysiology of combined vergences and saccades.

In Chapter 2 the question which cortical areas are engaged in the preparation and execution of exogenous saccades, combined convergences and combined divergences was addressed. We determined three cortical source pairs that were localized within (1) an anterior frontal area, (2) the occipital cortex and (3) the FEF. We hypothesized that the engagement of occipital cortex reflects its role in processing of visual stimuli that evoked the eye movements. Nevertheless, the difference in activity observed for the different eye movement types (larger for combined convergences compared to combined divergences and saccades and larger for combined divergences compared to saccades) strongly suggested that this activity may reflect processes related to depth cues. Similar

observations concerned the FEF. The engagement of both occipital cortex and FEF seems to be in line with previous studies, however the involvement of the anterior frontal area might be a residual eye movement artifact due to the correlations between source and EOG activities, and also due to the vicinity of the eyeballs.

In Chapter 3 the same questions as in Chapter 2 about cortical correlates for the preparation and execution of different types of eye movements were posed, however we were specifically interested in endogenously triggered eye movements: saccades, combined convergences and divergences. In this study also two regional sources were determined, which were localized within FEF and occipital cortex. Similarly to the experiment on exogenous eye movements, the preponderance of stimulus- compared to response-locked activity was also observed. For the FEF, also increased activity was observed for both vergence conditions compared to saccades, which strongly suggests that this area is engaged in processes necessary to prepare vergences, i.e., processing of retinal disparity. Interestingly, in contrast to the study on exogenous eye movements, endogenous saccades and combined vergences activated occipital cortex in a comparable way, which suggests that the engagement of occipital cortex does not depend on eye movement type. Therefore, it may be hypothesized that this activity reflects stimulus processing or working memory processing. The latter hypothesis results from the experimental design, since the difference between the first experiment on exogenous eye movements (where differences between conditions were not observed) and the second experiment on endogenous eye movements (where differences between conditions were observed) concerned the need to remember the meaning of the color cue that indicated the direction of the following eye movement.

In summary, it seems that different types of eye movements: saccades, combined convergences and divergences engage the same cortical regions. Moreover, the engagement of cortical structures seems to be also independent of whether the eye movements are internally or externally triggered. These observations are in line with previous fMRI studies on exogenous and predictive (volitional) saccades and vergences, which suggested that indeed saccades and vergences involve similar brain resources [154, 168]. A possible explanation of the engagement of similar neural regions for saccades and vergences may be based on the findings which showed that pure vergence stimuli evoke the subjects' response, which very often contains not only pure vergence eye movements, but also saccadic eye movements [220, 221, 222]. Interestingly, also the process of reading, which seems to engage only saccades and fixations, is a complex

motor task, which requires horizontal, vertical eye movements, and also depth control. Vernet and Kapoula (2009) [223] observed changes in fixation disparity (divergent and convergent disconjugacies) during saccades and fixation. As both pure saccades and pure vergences base on interaction between both saccades and vergences, the engagement of the same brain sources for saccades and combined vergences observed in our experiments seems to be quite evident.

It should be noted that both the study by Alvarez et al. (2010) [168] and Alkan et al. (2011) [154] indicated also that despite shared brain areas, they observed a spatial differentiation between saccades and vergences within the FEF. They revealed a distinct location within FEF that was located more anteriorly for vergences as compared to the saccade-related FEF. These findings are in line with a previous study on macaques by Gamlin and Yoon (2000) [167], who previously reported that vergences activate an area anterior to the FEF activated by saccades. In our studies this differentiation may not have been observed due to the lower spatial resolution of the EEG.

In both experiments, it was a bit surprising to observe the preponderance of stimulus-locked activity relative to response-locked activity, which suggests that the involved cortical areas have a crucial role in the preparation of eye movements rather than their execution. Interestingly, the findings of previous studies that tried to explain the observed activity of cortical areas related to eye movements (whether they are engaged in motor execution or rather sensory preparation) were unclear. In the case of the FEF, the earlier mentioned study on rhesus monkey by Gamlin and Yoon (2000) [167] suggested that activity of FEF neurons is closely related to the eye movement per se which is not in line with the interpretation presented in the current dissertation. They tested FEF cells during monocular accommodative vergence trial and found the same activity of neurons as during binocular vergence task. A similar suggestion, that the FEF are related to the execution rather than stimulus processing was made by Van der Lubbe et al. (2006) [27], who observed a positive anterior lateralized component shortly before saccade onset. However, in the study by Van der Lubbe et al. (2006) endogenous saccades were elicited in two steps (two-step approach, see paragraph below) and the processes of preparation and execution of eye movements may have been better separated, which may have allowed to show this activity. On the other hand, Ferraina et al. (2000) [166] also recorded single neuron activity in rhesus monkey and they revealed that FEF neurons are sensitive to both near and far disparities in exogenous vergences, and thus are related to stimulus processing. Nevertheless, the presented interpretation that activity within FEF

reflects the engagement in stimulus processing, seems to be in line with the studies by Schiller and Tehovnik (2005) [119, 176] who suggested the presence of two streams – anterior and posterior, engaged in the control of reflexive saccades. Schiller suggested that both streams have a different role in saccades, since the anterior stream, which included cortical areas, is associated with stimulus processing, whereas the posterior stream, which included subcortical areas, is related with movement execution. These observations seem to be confirmed as well for the eye movements investigated in the presented experiments and may explain larger stimulus-locked activity compared to response-locked activity for determined cortical areas.

Although preparation of saccades and vergences engage similar cortical regions, different types of eye movements activate both occipital cortex (in the case of exogenous eye movements) and FEF (in the case of both exogenous and endogenous eye movements) to a varying degree. Together with the preponderance of the stimulus-locked compared to response-locked activity, it can be hypothesized that this generally larger activity observed for both vergence conditions may reflect processes related to specific eye movement type, i.e., processing of crossed disparity in case of combined convergences and uncrossed disparity in case of combined divergences.

It was also surprising not to observe an estimated source within parietal cortex. Previous studies clearly suggested that the parietal cortices have a crucial role in the preparation and execution of reflexive eye movements, mainly saccades, since they revealed that lesions of PPC resulted in increasing latencies of this type of eye movements in both human [110] and monkeys [211]. Moreover, on the basis of more recent findings it may be suggested that the PPC is strongly associated not only with exogenous saccades, but also vergences and combined eye movements [108, 109, 206]. All these TMS studies provided complementary results since they revealed that TMS over right PPC increased the latencies of almost all eye movement types, whereas TMS over the left PPC prolonged the latencies of right saccades, convergences and right convergences. Based on these findings, it was concluded that the PPC, especially the right PPC, is engaged in the processing of fixation disengagement. Moreover, as was mentioned in General introduction, previous studies on both eye movements and hand reaching in depth suggested that parietal cortex process the information related to disparity [21, 163, 164, 165]. Interestingly, in the case of a volitional saccade task – memory-guided saccades, TMS over the PPC during an early phase of the paradigm increased the percentage of error in amplitude for contralateral eye movements, which may indicate that the PPC is

involved in sensorimotor processing [147]. Moreover, results of fMRI studies [9, 207, 208] suggested that the parietal cortex is relevant for volitional saccades. On the other hand, lesion of the PPC did not affect volitional, but only reflexive saccades [107]. In conclusion, the engagement of the parietal cortex in exogenous eye movements (both saccades and vergences) seems to be rather clear (although the regional sources within parietal areas were not included due to the model which was built on combined convergences (see Discussion, Chapter 2), however, its engagement in endogenous eye movements needs further examination. Nevertheless, the discrepancies in the results related to engagement of parietal cortex in endogenous eye movements (mainly saccades) may be an effect of a functional overlap between preparation of eye movements and attentional orienting, as was indicated by Van der Lubbe et al. (2006) [27] (see Discussion, Chapter 3).

Behavioral results obtained from both experiments included latencies defined as the time interval measured from the stimulus onset to the eye movement onset. In our study on exogenous eye movements the participants were instructed to make an eye movement from the fixation LED to the target LED, which appeared in the periphery of subject's visual field. In the study on endogenous eye movements one stimulus was used that indicated the direction of the following eye movement, which also indicated when this eye movement had to be performed (to have conditions similar to those from first experiment – one stimulus which triggered eye movements). Thus, the participant was also instructed to make an eye movement from the fixation LED to the target LED, however in the case of endogenous eye movements, the target LED was chosen according to the color cue. The study on exogenous eye movements revealed that saccades were characterized by the shortest latencies, intermediate latencies were observed for combined divergences, whereas the longest latencies were obtained for combined convergences. The behavioral results of exogenous eye movements perfectly correspond with the cortical activity results, where the largest activity was observed for combined convergences, intermediate for combined divergences, and the lowest for saccades. In the case of endogenous eye movements, no major differences in latencies were observed (significant differences concerned only saccades and combined convergences). In the case of internally driven eye movements, we also can conclude that behavioral data and registered source activities provide partially complementary result, since we did not observe differences in source activity between eye movement types for occipital cortex, however the differences concerned activity within FEF (see previous paragraph or

Chapter 3). When we focus on differences in latencies obtained for exogenous and endogenous eye movements, we can clearly observe longer latencies for endogenous compared to exogenous eye movements and loss of differentiation in latencies between eye movement types in the case of endogenous eye movements. It seems, that there are no previous studies that aimed at a comparison of externally and internally triggered eye movements which was evoked in such similar way as in our studies. Nevertheless, we can refer our results to the previous most common comparison of externally and internally guided eye movements, i.e., studies on prosaccades and antisaccades. Studies clearly indicated that indeed antisaccades are characterized by longer latentcies than prosaccades [224, 225, 226], thus endogenously driven saccades have longer latencies than exogenously, which is also observed in presented experiments. The possible explanation of this prolonged reaction time for antisaccades was tested in the study by Olk and Kingstone (2003) [227]. They suggested that the factors leading to differences in latencies between prosaccades and antisaccades are oculomotor inhibition and attention reorienting from target location. Interestingly, they also rejected the suggestion of the previous research which attributed this difference to the fact that antisaccades are generated volitionally. Based on these findings, it can be hypothesized that differences between latencies of exogenous and endogenous eye movements may result from shifting attention, since in the experiment on endogenous eye movements, the subjects were instructed to choose the target LED volitionally (as in antisaccade task) based on the color cue of a central LED, which indicated where the gaze should be shifted.

One may argue whether two separate experiments being a part of a presented dissertation can be easily compared. Certainly, it would be better to compare exogenous and endogenous eye movements, which will be examined in one experiment. Although in the second experiment the conditions were similar to those from the first experiment, there are some changes in the second one, which resulted from the experiences from the first experiment. Firstly, in the experiment on the exogenous eye movements, we built a model on the response-locked data, and later to be able to better interpret the results, we compared response-locked with the stimulus-locked activity. We surprisingly observed the preponderance of stimulus-locked activity. As a consequence, in the experiment on endogenous eye movements, we firstly compared stimulus- and response-locked data and since we also observed the preponderance of the former, we decided to choose a model that was built based on stimulus-locked activity. Nevertheless, we also built a model for the response-locked activity and we did not observe significant differences between both

models. Therefore, it can be suggested that the model is not dependent on data which were used to create it and as a consequence direct comparison of models obtained for the first and second experiments can be made. Secondly, in the first experiment three types of eye movements were performed in a random order and in the second experiment each type of eye movement was performed in a separate block. This blockwise manipulation used in the study made the type of eye movement predictable for the participants, which might result in the blurring of differences in brain activity or latencies between eye movement types. Although at the beginning we used auditory and color cues which indicated the type of eye movements and its direction respectively to avoid the prediction which could affect the results, the participants were not able to perform this task, because they had a problem with remembering the meaning of all used cues. Therefore, for the future studies it could be advantageous to use experimental design, which will allow to avoid the prediction and will be easy for participant to complete it.

Finally, to keep a similar design of both studies, in the experiment on endogenous eye movements we used one stimulus (one-step approach), which indicated the direction of the following eye movement and was the go signal at the same time. This approach reflects the more natural viewing condition since it integrates preparatory and executive phases of the movements. Nevertheless, it does not enable differentiation between stimulus processing and movement execution in a two-step approach, where two stimuli are used, i.e., first which indicates the direction of eye movement and second which indicates the moment, when this movement should be performed. A one-step approach does not engage an additional process like working memory, which is necessary when directional and go signals are presented separately. Moreover, a one-step approach in endogenous eye movements was used, since it allows for more straightforward comparison of results related to endogenous eye movements with the results related to the exogenous eye movements, since in the case of exogenous eye movements both stimulus processing and execution happen simultaneously. Moreover, using one-step approach enables performing the stimulus-locked and a response-locked analyses.

In the presented experiments, discrete source analysis was used, and the cortical activation underlying ERPs data was described by regional sources. This approach has an advantage over the equivalent dipoles as it allows to create more stable models [86]. In the literature one type of distributed source localization methods – LORETA is also often used and is characterized as an approach which was shown to give satisfactory results in most cases [85]. Distributed source models also use regional sources or dipoles as the

basic components to model brain activity. However, this approach (in contrast to the approach used in the presented experiments) does not allow to reconstruct the activity from one location, since it is contaminated by activity from other brain areas. Moreover, the separation of activities of brain regions which are localized close to each other is not possible. On the other hand, the model built using discrete source analysis needs to be determined by a fitting procedure i.e., requires decision on the time intervals in which sources will be fitted and numbers of sources as well. The discrete source analysis approach has been criticized by some researchers, who emphasized that localizing the sources of ERP data requires lots of experience [48]. Nevertheless, the simulation study by Miltner et al. (1994) [228], in which nine researchers with various level of expertise were asked to localize the dipoles using BESA technique based on ERP waveforms, revealed that the grand-average location error was approximately 1.4 cm (SD = 1 cm). Also the study by Leahy et al. (1998) [229] who investigated the dipole localization accuracy showed that the average localization error for EEG was 7-8 mm. Moreover, studies showed also that source localization can provide reliable results in localizing the irritative zone in focal epilepsy [230, 231]. Interestingly, there is also study, which combined the dipole fitting with fMRI technique [232]. Although approaches used in the study by Menon et al. (1997) [232] allowed to combine high temporal resolution of ERPs and high spatial resolution of fMRI which significantly increased the understanding of the outcomes, it should be noted that the authors assumed a priori the correspondence between ERP and fMRI source location.

In the present dissertation, the brain areas related to exogenous and endogenous vergence eye movement were investigated. Although the conditions of both tasks were as similar as possible to compare the outcomes of both experiments, it is generally recommended to make a direct comparison of different types of eye movements, i.e., investigate them in one experiment. Such an approach enables to avoid the differences which are a natural consequences of performing two separate experiments (for more details, see paragraph above). Moreover, it would be interesting to subject the findings obtained in our studies to further analyses, for example to find the relationships between the brain structures responsible for eye movements preparation and execution by performing source coherence analysis, what can be done using BESA approach (see: [233]). Additionally, wavelets analysis also could be implemented to obtain various frequencies from EEG signal and analyze how it changes over time [234]. Moreover, also determination how stimulation of indicated brain regions would affect different types of

eye movements may be helpful to better explain the role of these areas in eye movement preparation and execution.

CONCLUSIONS

In conclusion, the experiments which are part of the presented dissertation revealed that two cortical areas: occipital cortex and FEF are responsible for the preparation and execution of exogenous and endogenous saccades and combined vergences. The preponderance of stimulus-locked activity suggests the engagement of both areas in stimulus processing rather than motor preparation. Due to the differences in FEF activity observed for saccades and combined eye movements, the possible interpretation of the role that FEF has is the engagement in the processing of retinal disparity. Similarly, activity within occipital cortex in the case of exogenous eye movements suggests the engagement of this area in disparity, whereas in the case of endogenous eye movements activity within occipital cortex seems to reflect stimulus or working memory processing, as the differences between different types of eye movements were not observed. The summary of the roles which cortical areas have in the preparation and/or execution of reflexive and volitional vergences based on previous and presented studies is shown in Table 7.

The outcomes of the presented studies also emphasizes the necessity of implementing the procedure to compare stimulus- with response-locked activities when interpreting of the role of brain areas related to eye movements (possibly, this approach could be helpful also in other motor tasks). The implementation of such a procedure may also be interesting in the case of the antisaccade task, since the preparation of antisaccades requires the processes of higher-order cognitive control, which engage different cortical areas.

Table 8. Summary of the roles of different cortical brain areas in the preparation and/or execution of reflexive and volitional vergence (FEF – frontal eye field).

Cortical area	Role
Occipital cortex	Processing of retinal disparity in exogenous vergences
	Stimulus processing in endogenous vergences
	Processing of working memory in endogenous vergences
FEF	Processing of retinal disparity
Parietal cortex	Fixation disengagement in exogenous vergences
	Processing of retinal disparity

The outcomes of the presented experiments increase the basic knowledge underlying the functional anatomy of the eye movements which are relevant for 3D perception. Moreover, the results are crucial for a better understanding of the most complicated and the least known human system – the central nervous system. Nowadays, when average lifespan significantly increases and all kinds of neural diseases from cerebrovascular accidents to neurodegenerative diseases are more and more ubiquitous, a better understanding of human neurophysiology can directly influence a patient's outcome.

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FIG. 1. THE GRAPH REPRESENTS RELATIVE VISUAL ACUITY ACROSS THE HORIZONTAL VISUAL FIELD. THE AREA BETWEEN THE DASHED LINES REPRESENTS THE VISUAL ACUITY RELATED TO FOVEAL VISION. THE PICTURE REFLECTS HOW THIS DECREASE IN VISUAL ACUITY AFFECTS THE NATURAL VIEWING CONDITION (AFTER [7]). 17

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APPENDICES

APPENDIX 1

Poznań, 7.10.2021

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Author contribution statement

With regard to the paper "The engagement of cortical areas preceding exogenous vergence eye movements", published in the year 2018 in PLOS One, I estimate my own contribution to this paper at 70%. My work consisted of adjusting the device with LEDs used in the experiment, programming the experiment in Presentation software (with the support of the supervisor prof. UAM dr hab. Anna Przekoracka-Krawczyk), performing optometric examination to qualify participants for the study, performing EEG recordings, performing EEG analyzes (according to supervisors' indications), performing statistical analyzes (according to supervisors' indications), writing the manuscript (according to supervisors' comments).

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APPENDIX 2

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APPENDIX 6

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