The role of the cerebellum in oculomotor selection

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Summary of the proposed research

(*please provide in 100 words a summary of the proposed research in English*)

Vision is the dominant percept of humans. We constantly make eye movements to analyse our environment and determine what actions need to be taken and prepared for. Oculomotor response selection is, therefore, crucial to our survival. Although it is known that the cerebellum (CB) plays some role in correctly guiding oculomotor selection it is unclear what its contribution is. In this project the hypothesis is investigated that the CB monitors the integration of exogenous and endogenous information in saccade generation. We will combine fMRI and eye-tracking in a recently validated method to link neuronal and behavioural consequences in one framework.

Word count: summary 100 *(max. 100)*

Keywords

(max. 6 keywords that characterize your proposal. Keywords will be used to track reviewers)

Oculomotor selection; cerebellum; top-down; bottom-up; fMRI; eye tracking; 7 Tesla

Research topic

Maximum 2,000 words (about 4 pages) for sections 8a (topic) an 8b (approach) together, including footnotes and illustrations but excluding literature references. See also the description of the criteria in the brochure.

Oculomotor selection is the process which determines where we look at any given time. If we cannot make an eye movement (saccade) to an informative location in our field of view we would get lost in a blur of visual input. Therefore oculomotor selection is fundamental to our ability to survive. Most models of oculomotor selection focus on the cortex in explaining the mechanisms underlying oculomotor selection. The cerebellum (CB), although it contains about half the neurons in our brain and is impaired in many neurological diseases involving oculomotor problems, is largely neglected. Here, a project will be proposed that focuses on the role of the CB in oculomotor selection.

Oculomotor selection is driven by information gathered from peripheral vision [1] and other perceptual channels e.g. audition [2]. The ultimate selection of the goal of our next eye movement is the result of different environmental and internal influences. The process that is said to underlie oculomotor selection is competitive integration. Each item in the outside world (often called bottom-up information) evokes a peak of activation in a saccade map. These peaks are modulated by internal goal-driven factors (also called top-down information). The location that has the highest activation wins the competition and is the goal of our next eye movement [3]. It is known that the CB contributes directly to saccade generation via its connections to the superior colliculus (SC) which is considered the locus of integration of top-down and bottom-up information, the prefrontal cortex (PFC), where higher order cognitive processes take place and to the brainstem, that serves as a relay station for signals to and from the eyes [4]. This implies that the CB, in exerting its influence on saccade generation, employs both top-down and bottom-up information and positions the CB, like the SC, as a point of interaction between endogenous and exogenous components in oculomotor selection. This idea, however, has, to date, received little empirical attention. Although traditional models of saccade generation have incorporated the CB, these models posit different modulatory mechanisms for the CB. For instance, the model for saccade generation by Douglas Munoz [5] and the computational model proposed by Meeter and colleagues [6] both incorporate the CB. But, according to Munoz the CB exerts an excitatory influence on the reticular formation whereas in the Meeter model the cerebellum has an inhibitory influence on the SC neurons and the brainstem omnipause neurons [7]. A third model, the feedforward model of cognitive control in the CB by Ramnani [8], proposes how the CB, analogue to its role in motor control [9], contributes to higher cognitive functions. These three models provide a solid conceptual framework in which the CB can operate as a modulatory unit in oculomotor selection.

It is proposed that the dominant role of the CB is regulating the response to discrepancies between the expected outcome of an action and the actual outcome of an action, to essentially ask the important

question: did I do what I meant to do? The expected outcome is compared to the proprioceptive feedback from the central nervous system and other perceptual channels. In order to compute the expected outcome of a planned action it is hypothesized that the CB utilizes a similar mechanism for competitive integration as the SC. This holds three consequences for the role of the CB in oculomotor selection. First, the CB integrates top-down and bottom-up factors in order to predict the outcome of a response. Second, the predicted outcome is compared to the actual outcome of the response. Third, in case of a discrepancy the CB interferes by making small online corrections on the saccade (a 'short-term' role) and updating its internal model on which future predictions are based (a 'long-term' role) [10]. These internal models are, via the thalamus, also relayed to the PFC for better higher order planning in future situations. This cerebellar role implies that e.g. overshooting a target or mistakenly selecting a target that is not informative for your task, will trigger activity in the CB. It also implies that, upon adapting to the requirements of a task (learning), activity in the CB should change. These implications are corroborated by experiments with monkeys by Optican and colleagues [11]. They find that monkeys with a cerebellar lesion, depending on the locus of the lesion, lose the ability to correct the amplitude of a saccade to a target after repeated off-target saccade landings (long-term adaptation) or lose the ability to make a corrective saccade when the eye is drifting away from the target (short-term corrections). Lesion studies in humans show that, for instance, overshooting the target of a saccade (hypermetria) is a hallmark of cerebellar defects, especially if the fastigial nucleus or its projections are involved [12,13]. Also, the ability to adjust saccade amplitude in response to a changing visual environment (e.g. when putting on glasses) and gaze stability can be affected by cerebellar disease [14]. Anatomical studies show the existence of pathways that are essential for such a cerebellar role. For instance, Crus I and Crus II connect to the PFC [8], the oculomotor vermal regions IV to VI area connect to the motor cortex [15], the deeper nuclei such as the fastigial nucleus connect to the SC and the floccular region connects to the brainstem [4]. It is therefore expected that, depending on the task demand and the required top-down and bottom-up contribution, different cerebellar areas show activation.

I, therefore, propose that the CB is essential in monitoring the result of competitive integration of top-down and bottom-up factors and is responsible for short-term corrections and long-term learning and, secondly, that the activation in the CB is anatomically separated consistent with its different anatomical projections.

Approach

The experimental approach will show the importance of the CB for monitoring the outcome of oculomotor selection and the need to acknowledge this brain region in clinical research in order to

develop treatment and therapies for patients with oculomotor problems. This project will apply a wide range of behavioral oculomotor selection paradigms to establish which cerebellar regions are involved in oculomotor selection. In order to investigate the cerebellar role, high resolution functional magnetic resonance imaging (fMRI) will be combined with online eye tracking measuring e.g. saccade endpoint, saccade trajectory and reaction time.

The fMRI data will be acquired on the state-of-the-art 7 Tesla (7T) MRI scanner in the University Medical Center in Utrecht (UMCU). Until recently it has been very difficult to obtain imaging data from the CB due to its high density and difficult anatomical location that embeds the region in blood vessels, fat, bone, muscular tissue and air cavities that produce many artifacts. The past year a new method has been developed using dual transmission and multi-element surface coils close to the head to reliably image the cerebellum at high resolution (up to 0.5 mm^3) [16,17]. This resolution is high enough to visualize detailed anatomical features such as gray and white matter separations, folia, the vascular system and the smaller nuclei. By using fast acquisition sequences with sensitivity encoding (SENSE) [18] and three-dimensional segmented echo planar acquisition (3D-EPI) [19,20] spatial distortions are significantly reduced. This allows the detection of blood oxygen level dependent (BOLD) signal changes in response to different task demands in the dense, inhomogeneous and idiosyncratic anatomy of the CB. In collaboration with the Erasmus Medical Center in Rotterdam we have performed two successful pilot studies on saccade generation in the CB that combined fMRI and an MR-compatible eye tracker [17]. This combination allows us to make high quality images of activity related to saccade generation in the human CB.

The behavioral experiments will focus on inducing competition in oculomotor selection by manipulating bottom-up factors and top-down factors. Bottom-up factors will be manipulated, for instance, by changing the target location after saccade initiation (saccade adaptation paradigm, fig. 1a) or introducing pre-potent distractors (oculomotor capture paradigm, fig. 1b). Top-down manipulations includes influencing the expected target location (rule-learning paradigm, fig. 1c) and introducing a difficult task instruction in which reflexive and voluntary control of saccades are in competition (anti-saccade paradigm, fig. 1d). In these experiments the short-term and long-term effects of oculomotor selection in the CB will be analyzed. It is also known that saccade reaction time (SRT) has a large influence on the extent to which top-down information can influence oculomotor competition [21,22]. The time-course of oculomotor competition in the CB will therefore be investigated by manipulating the timing of stimulus-driven and goal-driven saccades (global effect paradigm). These experiments will establish which cerebellar regions show activation due to oculomotor competition and what their role is in short-term and long-term control of oculomotor selection. Finally, in collaboration with Dr. Neggers (UMC Utrecht), it will be attempted to manipulate competitive integration in a transcranial magnetic stimulation experiment (TMS) targeting the cerebellar regions that have shown activity in

the behavioral experiments (e.g. saccade adaptation and global effect paradigm). The results can be used to reappraise the models by Munoz [5], Meeter and colleagues [6] and Ramnani [8].

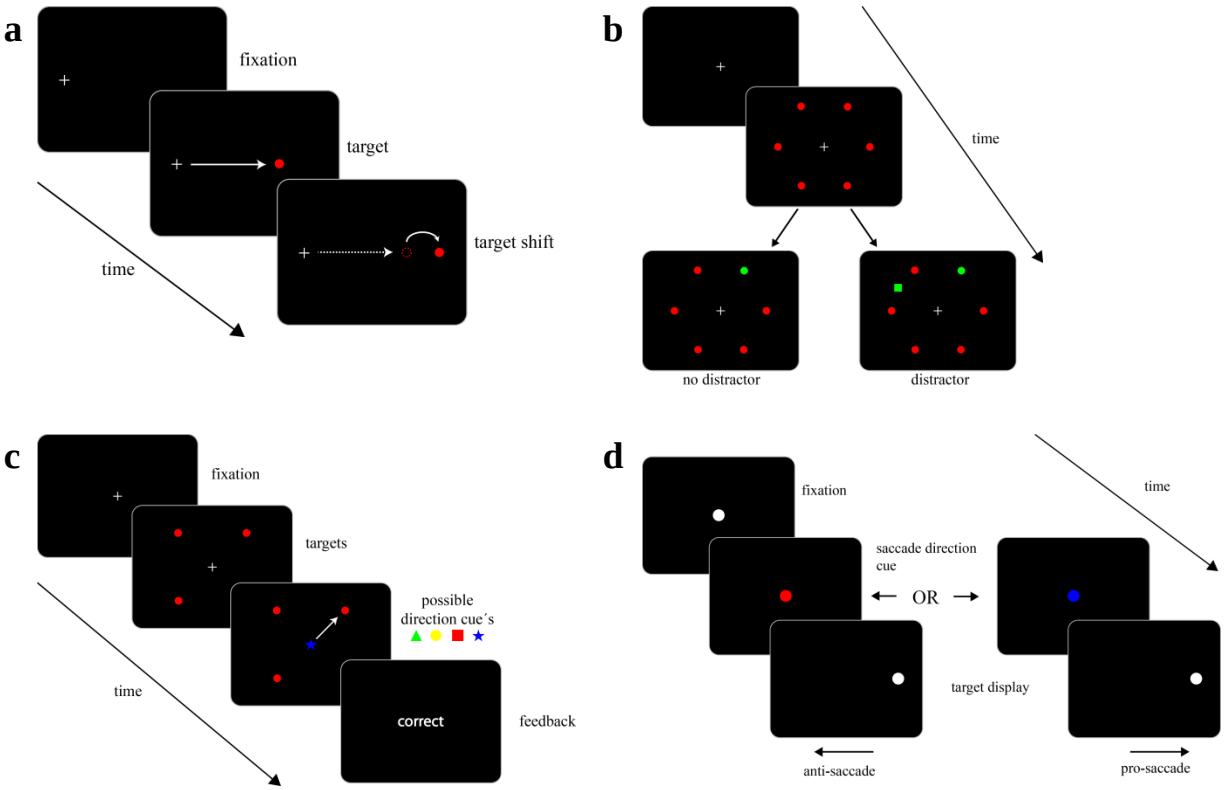

Figure 1: saccade adaptation task (a), oculomotor capture task (b), rule learning task (c), anti-saccade task (d).

The experimental approach will systematically focus on the research hypothesis by a four angled approach. First, a baseline of saccade activity in the CB will be established by performing an *anti-saccade task* (fig. 1d) [23,24]. This experiment tests the flexible control we have over oculomotor selection. It will answer the question which cerebellar regions are active during reflexive saccades towards a target (pro-saccades), voluntary saccades away from a target (anti-saccades) and erroneous reflexive saccades (making pro-saccade where an anti-saccade is required). In a second series of experiments the focus will be on investigating the role of the CB in online oculomotor corrections (short-term role). To this end an *oculomotor capture task* (fig. 1b) [25] and a *double step task* [26] will be conducted. The oculomotor capture task will show the effects of pre-potent bottom-up distractors on saccades that land on the distractor (capture saccades) and saccades that are corrected mid-flight (turnaround saccades) in contrast to correctly executed saccades. The double step task will shed light on the effects of a failure to inhibit reflexive saccades to a distractor by contrasting the corrected saccades (compensated saccades) against the saccades that are not corrected (non-compensated saccades) and reveals activity related to a quick corrective saccade in case of an initial error (double

step saccade). The third series of experiments will unravel the long-term role of the CB in oculomotor selection. The central question will be how cerebellar activity changes when we adapt oculomotor selection under changing conditions. A *saccade adaptation task* (fig. 1a) [27] will show the process of adapting saccade amplitude when the saccade target jumps to a different location after the initiation of a saccade. A *rule-learning task* (fig. 1c) [28] in which rules have to be learned based on feedback will focus on top-down components in oculomotor selection such as expectation and experience. A *global effect task* [22] will establish whether activity transfers to other anatomical regions depending on the amount of voluntary control we have over oculomotor selection. Finally, TMS can be applied to stimulate the cerebellar regions that have been identified in the previous experiments. This non-invasive method can be used to either suppress or enhance the contribution of top-down and bottom-up components in cerebellar monitoring of competitive integration. For instance, inhibition of top-down components should alter the voluntary control over saccades and increase the percentage of capture and turnaround saccades in the oculomotor capture task [29]. Or, during an adaptation task, the ability to adapt to a target shift can be flawed by applying TMS to regions that are involved in improving internal cerebellar models based on bottom-up information [30].

Table 1: The primary focus of the proposed experiments. Relevant cerebellar regions for each category are in italics. global

	Short-term role (online corrections)	**Long-term (learning and adapting)**
	Fastigial nuclei	***Crus I and II***
Bottom-up factors (reflexive)	Oculomotor capture task (fMRI)	Adaptation task (fMRI)
Floccular region	Double step task	Adaptation task (TMS)
	Oculomotor capture task (TMS)	
Top-down factors (voluntary)	Anti-saccade task	Rule-learning task
Cruss I and II		
Time-course	Global effect task	Global effect task

Word count: Research Topic 929

Word count: Approach 1065

Total word count Research Topic and Approach: 1994 *(max. 2000 words)*

Time plan

Give a practical timetable over the grant period, max. half a page.

		2014	2015			2016			2017	
I	Anti-saccade experiment									
	Article 1 – Oculomotor control in the CB									

II	Oculomotor capture experiment									
	Double step experiment									
	First knowledge exchange meeting									
	Article 2 – Online monitoring and correction of oculomotor selection in the CB									
	Present at ECEM 2015									
III	Saccade adaptation experiment									
	Rule-learning experiment									
	Article 3 – The role of the CB in learning and adaptation									
	Global effect experiment									
	Second knowledge exchange meeting									
	Present at SFN 2016									
	Article 4 – The time course of bottom-up and top-down cerebellar activity									
IV	TMS									
	Article 5 – TMS and oculomotor selection									
	Present at HBM 2017									
	Third knowledge exchange meeting									
	Write dissertation									

Dissertation, scientific output and output related to knowledge utilization

	Output	Number	Expected year of publication
X	Articles in refereed journals	5	2014 (1), 2015 (2), 2016 (2)
☐	Articles in non-refereed journals		
☐	Books		
☐	Book chapters		
X	Dissertation	1	2017
☐	Conference papers		
Output related to knowledge exchange and impact (please specify)			
☐	Professional publications		
☐	Other scientific output		
☐	Publications aimed at general public		

Knowledge exchange and impact

Address the potential and implementation of knowledge exchange and impact (Max. 500 words or no more than 1 page, for assistance see paragraphs 4.2 and 6.2 of the brochure)

Potential

- *Describe what the project's contribution is to society and/or to other scientific domains;*
- *Describe who will benefit from the project's results and why;*

Implementation

- *Describe how the project's result will be disseminated of potential users;*
- *Describe, if available, the project team's expertise on knowledge exchange and impact and how it will be deployed to enhance knowledge exchange and impact of results;*
- *Describe how potential users of the project's results will be included;*
- *Describe when the project's result are ready for use by third parties within and outside the academic sector;*

In the case of research that does not lend itself to knowledge utilisation as described in the aforementioned terms, the researcher is requested to briefly explain why he/she believes that knowledge utilisation is not applicable to the proposed research. In that case you don't need to address implementation.

Clinical applications

Providing better insight and knowledge about the cerebellar contributions to the oculomotor selection is important to developing new and better diagnosis, therapy and treatment for a wide range of patients with congenital and acquired cerebellar malfunctions. Among which:

Cerebellar lesions [31]

Huntingtons desease [32]

Cerebellar atrophy [33]

Joubert syndrome [34]

Fetal Alcohol Spectrum Disorder [35]

Through yearly knowledge exchange meetings clinical researchers will be kept informed about the result of this project. The project partners will actively approach researchers that might benefit from a knowledge exchange. Two researchers, Dr. T. Nijboer (revalidatie centrum De Hoogstraat) and Dr. H. Kroes (UMCU, medical genetics), have already expressed their interest and have been recruited for attending the meetings. To embed the empirical knowledge in a clinical context the project partners are available for advice on setting up research that involves cerebellar patients.

Dissemination of knowledge

This project is a cooperation between Utrecht University and the University Medical Center Utrecht where the 7 Tesla MRI facility is located. The project is also a knowledge exchange between the project partners and the Erasmus Medical Center in Rotterdam that assisted in developing the fMRI acquisition sequences and eye tracking validation.

Results of this project will be presented at European Conference for Eye Movements, Human Brain Mapping and the Society for Neuroscience conference.

Marketing

The method of combining (f)MRI and eye tracking that will be refined during the course of this project is especially relevant to neuromarketing research. Eye tracking has long since been a valued method of measuring consumers' responses to marketing stimuli. In recent years neuroimaging techniques have been added to the methodological repertoire of marketing researchers in testing the effectiveness of e.g. advertisement and product presentation. Combining eye tracking and imaging is a valuable and timesaving addition to the current repertoire. Also, the increased knowledge attained during this project about what 'captures the eye' and how exogenous and endogenous factors influence what we look at can be applied in product design and retail layout. In order to make methods and the acquired knowledge available to neuromarketing researchers results will be published in open access journals as much as possible.

Word count Knowledge exchange and impact: 357 *(max. 500)*

Summary of requested funding

Personnel	
PhD student	3 years full time including bench fee

Research costs	**In k€**
Scanning facilities	8.5
Adaptation of surface coils for imaging the PFC	1
Eye tracker supports to attach eye tracker to different coil setups	0.5
Total costs requested (k€)	**10**

The total amount of requested Research cost and Costs for knowledge exchange and impact cannot exceed 10,000 €. See also paragraph 3.2 of the brochure. Do not include the PhD candidate's expenses on attending conferences, costs on producing the dissertation and the defence ceremony, as these are covered by the bench fee.

Motivation for the requested budget

Please provide a motivation for the (specified) Research costs and Costs for knowledge utilisation mentioned above.

Research costs will comprise of the cost for:

- using the 7 Tesla MRI facility in the UMCU at 350 €/hour (8.5 k€)
- adapting RF coils used to image the cerebellum for use on other brain areas including the prefrontal areas by the UMCU coil lab (1 k€)
- eye tracker supports to attach the eye tracker to different coil setups fabricated by the medical technology department of the UMCU (0.5 k€)

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