Investigating brain activity patterns related to performing a Go/No Go task under cued and uncued conditions

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I Abstract

Parkinson's Disease is one of the most common neurodegenerative disorders worldwide. One of the symptoms of Parkinson's Disease is a decreased response inhibition ability. The current treatments for Parkinson's Disease, Levodopa and deep brain stimulation do not provide a way to improve response inhibition. Another possible treatment is known as cueing, a neuromodulation technique based on the presentation of external, rhythmical stimuli to the patient. Cueing has been shown to improve gait parameters of patients, so it might also have influence on the response inhibition ability of patients with Parkinson's Disease. However, its working mechanisms are not exactly known. Therefore, to expand the knowledge about the working mechanisms of cueing, the aim of the current study is to investigate the influence of certain types of cues on response inhibition.

Twenty healthy subjects performed a Go/No-Go task, a method of simulating response inhibition under the influence of three types of cues. Under the first of these conditions, the participants received No Cues, under the second they received Slow Cues with a frequency of 0.75 Hz, and under the last condition they received Fast Cues with a frequency of 3 Hz. During the performance of the task, the electroencephalograms (EEG) of the participants were collected, as well as their reaction times and the amount of mistakes they made. The EEG data was processed to find event related (de)synchronisations (ERD/ERS) and event related potentials (ERP) in response to either a Go or a No-Go stimulus. As a control condition for the reaction times, a Go-Only task was added to the experiment.

The reaction times and amount of mistakes that were made did not show significant differences between cueing conditions. The ERP has shown that the Go/No-Go task worked as predicted, but did not show any significant differences between cueing conditions when looking at N2 and P3 peak amplitude and latency. No significant differences between cueing conditions were found in the ERD/ERS.

On the healthy subjects, cueing did not have any effects. However, it was proposed that the role of the cerebellum was not to take over the response inhibition function of the basal ganglia, but provides a more supporting role. In patients with Parkinson's Disease, this supporting role might become more leading as the basal ganglia are defective. Cueing might provide a solution then for their problems with response inhibition as well.

II List of Acronyms

ANOVA Analysis of variance

DBS Deep Brain Stimulation

ECG Electrocardiogram

EEG Electroencephalogram/Electroencephalography

ERD/ERS Event related Desynchronisation / Synchronisation

ERP Event related potential

fMRI Functional magnetic resonance imaging

FOG Freezing of gait

GPe Globus pallidus externa

GPi Globus pallidus interna

ICA Independent component analysis

IFG Inferior Frontal Gyrus

KS Kolmogorov-Smirnov

N2 Negative peak located around 200 milliseconds in an event related potential

P3 Positive peak located around 300 milliseconds in an event related potential

PD Parkinson's disease

preSMA Presupplementary Motor Area

SNc Substantia nigra pars compacta

SNr Substantia nigra pars reticulata

STN Subthalamic nucleus

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1 Introduction

1.1 Parkinson's Disease

Parkinson's Disease (PD) is one of the most common neurodegenerative diseases worldwide. It is estimated that seven to ten million people suffer from the disease.[1] The cardinal symptoms of PD are brady- and akinesia, resting tremor, rigidity, and postural instability[2,3] and in later stages of the disease also freezing of gait (FOG). FOG is defined as "a brief episodic or marked reduction of forward progression of the feet despite the intention to walk"[4,5] and causes a lot of falls in PD patients. These symptoms are caused by the loss of dopaminergic neurons in the substantia nigra pars compacta (SNc) of the basal ganglia.[2,6,7] Due to the loss of these neurons, abnormal firing patterns arise, resulting in the aforementioned fundamental motor problems, but also in risk-taking behaviour, performing an action without reflecting beforehand, and the reduced capability to withhold habitual or pre-potent responses.[8–10] This is the result of a reduced response inhibition ability.

1.1.1 Response Inhibition

Response inhibition is the ability to successfully suppress inappropriate, irrelevant or suboptimal responses.[11] An example of response inhibition could be that someone is trying to cross the street, when unexpectedly a car comes around the corner. The initially planned action of crossing the street is suddenly inappropriate, as the situation is now dangerous. The person should stop and wait for the car to pass, before continuing crossing the road. The network that is responsible for response inhibition consists out of the inferior frontal gyrus (IFG), the presupplementary motor area (preSMA) and the subthalamic nucleus (STN).[12–14] Response inhibition is initiated in the cortex in the IFG and preSMA via beta oscillations (13-30 Hz), that activate the STN.[14] These areas are also part of the hyperdirect pathway, which is used in the basal ganglia-thalamo-cortical network to initiate or stop movement as smooth as possible.

1.2 Basal Ganglia-Thalamo-Cortical Network

The basal ganglia-thalamo-cortical network, also known as the extrapyramidal system, is involved in preparation, timing, and execution of movements and consists out of the basal ganglia, the thalamus and the cerebral (motor) cortex. The basal ganglia consist out of the striatum, pallidum, STN, and the substantia nigra. Through sequential (in)activation of each nucleus, movement gets initiated or stopped as smooth as possible.[15,16] These sequences are activated through the direct, the indirect, and the hyperdirect pathways, which all start with activation of the motor cortex (figure 1).[15–18]

The direct pathway facilitates voluntary movements by disinhibiting the thalamus. In order to do this, first, the motor cortex excites the striatum with glutamatergic neurons. Then, under the influence of dopamine, originating from the SNc, the striatum inhibits both the substantia nigra pars reticulate (SNr) and the globus pallidus interna (GPi). The purpose of these structures is inhibiting the thalamus. Therefore, when they are less active, less inhibitory neurons will be active, which disinhibits the thalamus. The thalamus now excites the motor cortex even more, allowing movement to be performed.[16–18]

The indirect pathway normally suppresses (involuntary) movement by constantly inhibiting the globus pallidus externa (GPe). As the GPe has an inhibitory effect on the STN, the latter will become more active, stimulating the GPi and the SNr. By becoming more active, they will inhibit the thalamus, which has a inhibitory effect on the motor cortex, suppressing (involuntary) movement.[16–18]

The last pathway is the hyperdirect pathway, which is inhibitory and important for response inhibition. The cortex (e.g. the IFG and preSMA) excites the STN directly, activating the SNr and the GPi, just like in the indirect pathway. This will suppress the thalamus and therefore also the motor cortex. Together with the other pathways, this results in execution of the selected motor program, by cancelling competing and unwanted motor programs. [16,19,20]

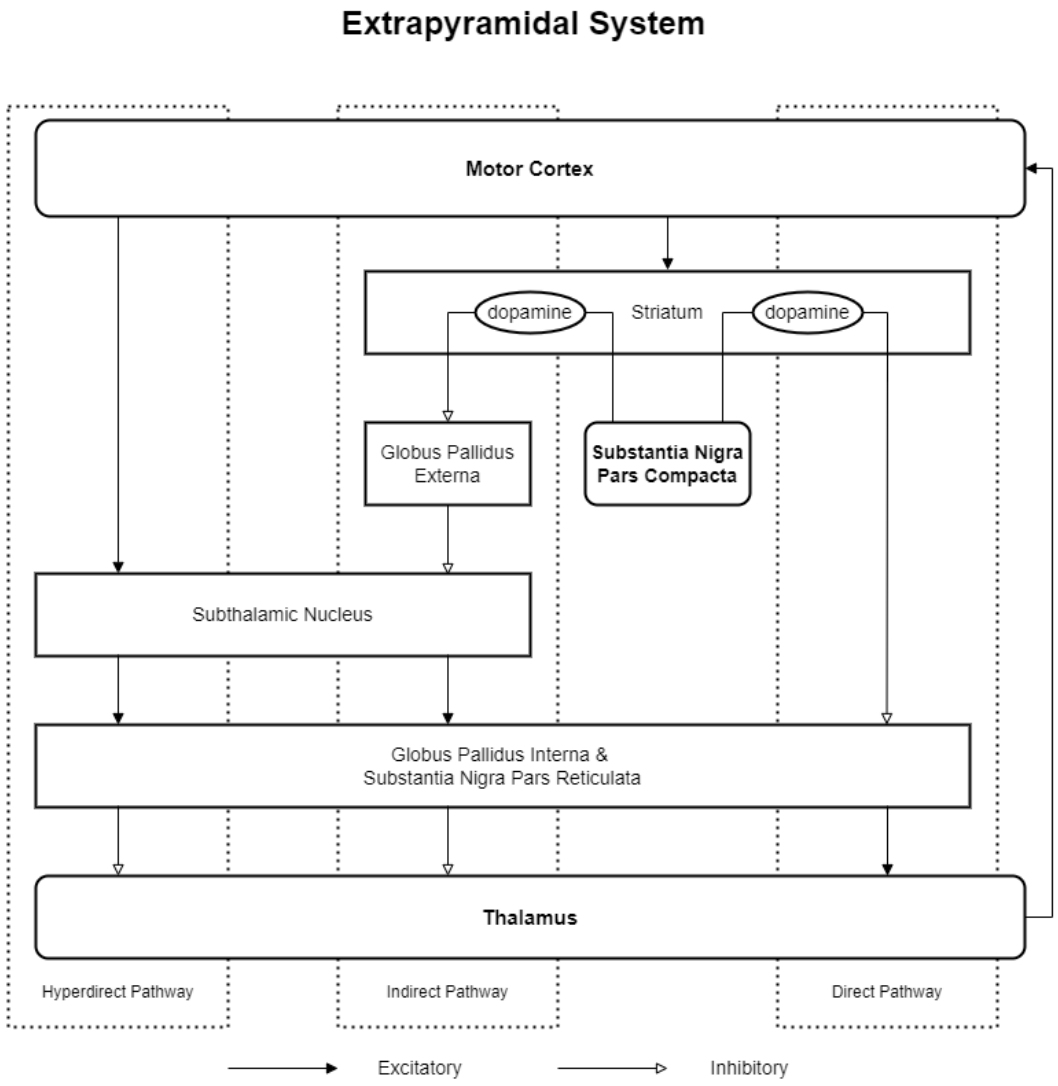


Figure 1: A schematic representation of the extrapyramidal system, showing the direct, indirect, and also the hyperdirect pathways. The result of the direct pathway is the disinhibition of the thalamus and therefore allows self-induced movements, whereas the indirect and hyperdirect pathways inhibit the thalamus, suppressing for example (involuntary) movements.

1.2.1 Center Surround Model

The model that describes how these pathways cooperate to execute selected motor programs, is called the center-surround model.[20] In the center-surround model, it is proposed that after a motor program is selected, first the hyperdirect pathway inhibits large regions of the motor cortex in the aforementioned manner.[20] This way, the motor cortex gets prepared for the activation of the new motor program. Right thereafter, the direct pathway inhibits the parts of the SNr and GPi that are associated with the new movement.[20] The thalamic projections of these areas become activated, allowing the selected motor program to be performed. Finally, the indirect pathway reaches the SNr and GPi, terminating the selected motor program at the correct time not to exceed the goals of the selected motor program.[20] In the healthy situation, this model shows that movement is initiated, executed, and terminated in the correct sequence with the proper timing. At the same time, competing motor programs from the surrounding area are suppressed and cancelled.[20]

This model can also be used to explain the symptoms of PD patients. Hyperactivity of the STN causes the hyper- and indirect pathways to suppress larger areas of the thalamus and therefore of the cortex.[10,21] Moreover, smaller areas get disinhibited by the direct pathway for a shorter period of time, leading to the brady- and akinesia symptoms of PD patients.[10,15,16,21] Besides, in PD patients, a pathological synchronisation of the beta band activity is found in the basal ganglia.[14,22,23] These high power beta oscillations might block movement inducing high-frequency oscillations, causing the patient to get 'stuck' in their current motor program.[23,24] This could explain why movements get initiated slowly, but it could also explain a reduced response inhibition ability, as patients cannot easily switch from their suddenly inappropriate habitual, prepotent response.

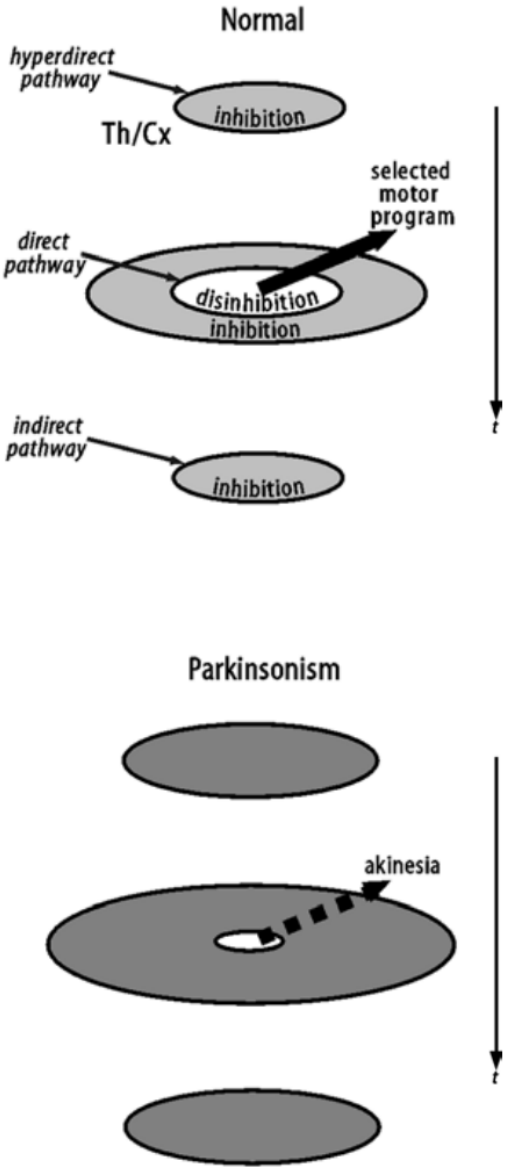


Figure 2: Top: center surround model for the healthy situation. First, the hyperdirect pathway inhibits the thalamus (Th) and the motor cortex (Cx). Next, the direct pathway disinhibits the area for the selected motor program. Finally, the indirect pathway inhibits the area again. Bottom: center surround model for PD patients. The stronger signals through the hyperdirect and indirect pathway suppress larger areas, whereas the signal through the direct pathway disinhibits a smaller area, resulting in at least the motor symptoms of PD. Figure adapted from[21].

1.3 Treatment Options

Currently, PD patients can be treated in multiple ways. The most common form of treatment is dopamine replacement with Levodopa.[25,26] Levodopa, a dopamine precursor, greatly reduces the motor symptoms of the patient when it reaches the cerebral tissues and gets converted to dopamine. At least in early-stage PD, this therapy is an effective treatment for motor symptoms, decreasing pathological

beta oscillations, and non-motor symptoms, such as response inhibition.[22,24,27] With progression of the disease however, Levodopa loses its effect for non-motor symptoms, and higher doses are required as the responses to this therapy become unpredictable.[27–30] For instance, symptoms may return before the next dose is scheduled or symptoms may not improve at all despite administration of a dose.[25] Besides, as a side effect of the medication patients might develop other motor complications, such as Levodopa-induced dyskinesia, where they show involuntary, erratic movement.

Deep Brain Stimulation (DBS) of the STN offers a more effective treatment, which can greatly reduce the requirement of Levodopa.[31] However, this procedure is highly patient specific and requires complicated, invasive surgery and gets only provided to carefully selected patients based on their symptoms and response to their medication.[32] Ballanger et al. have found that DBS of the STN, besides significantly improving the motor symptoms of PD patients, increased the error rate of patients in a response inhibition task.[33] They concluded that the modulation of STN hyperactivity with DBS made patients more impulsive. They also hypothesised that akinesia and impulsivity may be closely related and that the response inhibition network plays an important role in both functionalities.[33] This reinforces the hypothesis about high power beta oscillations from section 1.2.1. However, this makes that both medication and surgery are great options for relieving the motor symptoms of PD patients, but have no positive effect on their response inhibition abilities.

1.3.1 Cueing

Another, more accessible option could be cueing. Cueing is a neuromodulation technique where rhythmic and repetitive auditory or visual stimuli, named cues, are presented to the patient.[34–37] Previous research have shown that cueing can be beneficial for the motor symptoms of PD patients, as it increases gait velocity, decreases gait variability, and reduces the amount of FOG episodes.[34–39] However, the exact mechanisms behind cueing remain unknown.

One hypothesis is that cueing improves the internal timing mechanisms so that under the influence of or in response to cues the patient will adapt their movements according to their rhythm.[40] An example of which could be patients who adjust their walking patterns to the beat of a metronome.

A second hypothesis is that cueing improves attention and task prioritization.[8,15,41] Cueing possibly shifts the attention to the task, which causes a shift from automatic, habitual motor control towards goal-directed motor control. This could facilitate decision making and the selection of the more appropriate response, instead of the fast, habitual, pre-potent response.[8,10,41] This is important in response inhibition, because successfully inhibiting an action cannot be done without any attention to the task at hand.[42]

A third hypothesis could be that cueing might be effective due to the involvement of the cerebellum. This hypothesis might be supported by the other two mentioned before. Normally, the cerebellum is involved in attention and the planning, initiation, control, and correction of voluntary movement. When the cerebellum becomes active, its cortex inhibits the nucleus dendata, the largest structure connecting the cerebellum to the rest of the brain (figure 3). The nucleus dendata in turn stimulates the thalamus and therefore also the premotor and parietal cortices, which are responsible for the selection and coordination of movements respectively.[16,43–45] These cortices provide, via the pons, feedback to the cerebellar cortex. If cueing activates this circuit, it could improve both attention and the internal timing of PD patients by bypassing the defective basal ganglia.[46]

However, the effect of cueing is frequency dependent. Previous research in healthy subjects have shown that the cortical areas associated with the cerebellar pathways, i.e. the premotor and parietal cortex, only showed increased activation during cueing with a more discrete frequency below 2 Hz.[47–50] At the same time, decreased activity was found in the cortical areas associated with the basal ganglia, i.e. the

prefrontal and frontal cortex, primary and supplementary motor cortex, and the primary somatosensory motor cortex.[16,43,44] As these areas are associated with the basal ganglia, they are involved in preparation, timing, and execution of movements as well. Moreover, in the healthy situation, they are also responsible for action selection and response inhibition. When the researchers cued with a more continuous frequency at 2 Hz, the cortical areas associated with the cerebellum showed decreased activity, whereas the areas associated with the basal ganglia showed increased activity.[47–50] The cueing frequency of 2 Hz might therefore be the tipping point between the basal ganglia pathways and the cerebellar pathways. This might, together with the fact that the basal ganglia of patients with PD are defective, explain why cues with a frequency below 2 Hz are more effective in improving the gait impairments of PD patients, than cues with a frequency above 2 Hz.[51–54]

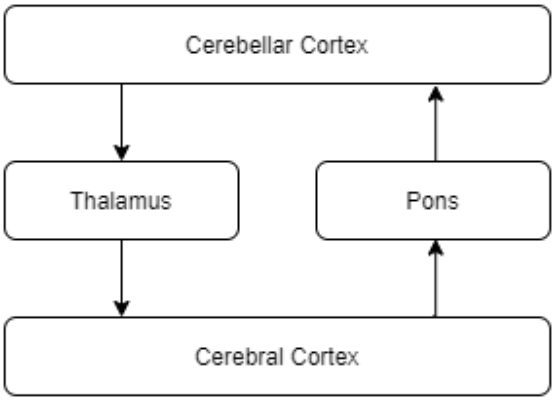


Figure 3: Schematic representation of the cerebellar pathway. The cerebellar cortex activates the thalamus via the nucleus dendata. In turn the premotor and partietal cortices are activated. Via the pons, feedback is provided to the cerebellar cortex.

So, cueing is proven to be effective in guidance of repetitive movements, possibly by improving internal timing mechanisms, increasing the attention to the task, bypassing the defective basal ganglia by using the cerebellar pathways, or any possible combination thereof. However, it still needs to be shown that cueing is effective in improving response inhibition.

1.4 Evaluating Response Inhibition

1.4.1 Go/No-Go Task

There are several experimental tasks to measure response inhibition. A commonly used one is the Go/No-Go task.[55,56] In the Go/No-Go task a subject is confronted with one stimulus, either stating 'Go' or stating 'No-Go'. In response to these stimuli, the subject has to perform an action correctly and as quickly as possible (i.e. Go stimuli) or withhold this action (i.e. No-Go stimuli).[26] Due to the command to react as quickly as possible to Go stimuli, the initial planned action of the subject will be to respond. This planned action will become even stronger by providing more Go stimuli than No-Go stimuli.[26,55] When the subject suddenly gets confronted by a No-Go stimulus, this initial planned action becomes inappropriate, simulating response inhibition.[8]

By using a Go/No-Go task, the behaviour, i.e. the reaction times and the accuracy, of the subject can be measured. The reaction times are defined by the response times to Go stimuli, whereas the accuracy is defined by the amount of times where the subject mistakenly responds to a No-Go stimulus. This enables the quantification of both the subject's action selection ability and their response inhibition ability.[9,57]

1.4.2 Electroencephalography

Response inhibition can clearly be visualised in event related potentials (ERP) of the subject.[55,58] An ERP is a time locked average of the electroencephalogram (EEG) of the subject in response to repeated application of specific stimuli.[59] It is important to administer multiple stimuli of the same type, because of the low amplitude of a single response. The pattern of the response is very regular, so by taking the average of multiple signals, the irregular rhythms cancel each other out, clearly showing the task-specific ERP of the subject.

The first important peak of the ERP in response to a Go/No-Go task is the N2 peak. This is a large negative peak (figure 4), typically evoked around 200 milliseconds after stimulus onset. The N2 peak is the

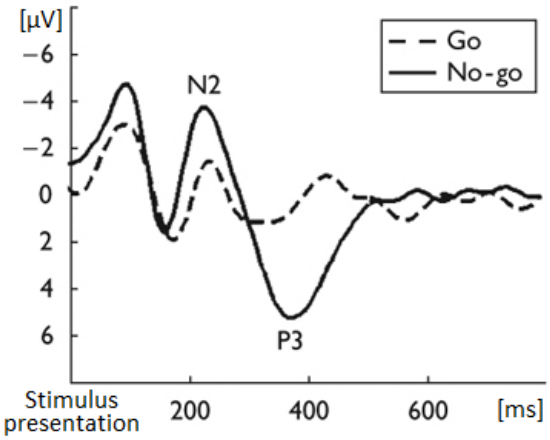


Figure 4: An example of the ERP (Cz electrode) in response to a visual Go stimulus (dashed line) or to a deviating visual No-Go stimulus (continuous line). In response to the No-Go stimulus, the N2 peak can be found around 200 ms after stimulus presentation and the P3 peak can be found right thereafter. This figure is adapted from[60].

visualisation of the processing of deviant stimuli and should therefore be larger when a No-Go stimulus was presented.[58,59,61] This is due to the fact that subjects are biased towards Go stimuli, which automatically makes the No-Go stimuli unexpected and therefore deviant from the initially planned action.[62] The P3 peak comes directly after the N2 peak and is a large positive peak around 300 ms after stimulus onset. The P3 peak indicates that a stimulus is being processed, the task relevance is being evaluated, and the working memory is being updated.[61] The amplitude of both peaks is correlated with the strength of response inhibition.[55,61–63]

In the frequency domain, the event related (de)synchronisation (ERD/ERS) can be analysed. These are time-locked, frequency specific fluctuations in the power of the EEG and consist out of either a decrease (desynchronisation), or an increase (synchronisation) with respect to the power during a baseline. With other words, the ERD/ERS shows for a certain frequency band which cortical areas become more or less active in response to a stimulus[64].

The ERD/ERS can be calculated per frequency band. The four frequency bands that are of interest are the theta, alpha, beta, and gamma bands. The theta band (3-7 Hz) is related with for instance a drowsy state of mind, but if the theta band is found in the frontal regions of the brain, it is associated with cognitive control.[65] During the Go/No-Go task, a theta band increase can be observed in the frontal regions when comparing the response to No-Go stimuli with the response to Go stimuli. No-Go stimuli are related to response inhibition, therefore it is proposed that response inhibition is also related to the theta band increase.[65] The alpha band (7-13 Hz) is associated with cortical involvement, as a high power would indicate cortical idling.[65] Besides this, an increase in alpha power is also associated with inhibition of movement.[66] The beta rhythm (13-30 Hz) is often associated with processing sensory information and planning of movement.[16,67,68] Beta power has been shown to decrease preceding Go stimuli. This decrease is terminated early in response to No-Go stimuli.[69] Finally, the gamma rhythm (30-70 Hz) is often associated with cortical activity during dynamic tasks.[16,68] Increases in gamma power were found during voluntary movement, but inhibiting those movements did not seem to have an effect on gamma power.[69] Cueing, on the other hand, could have an effect on both the beta and gamma bands, considering those bands are associated with processing sensory information and performing dynamic tasks.

1.5 Research Goals

To summarise, for the decreased response inhibition ability of PD patients, there still is no effective treatment. Levodopa does not seem to improve the ability and DBS might have a negative impact on the normal functions of the STN.[10,28] The effects of cueing on response inhibition, however, are yet to be studied. Considering the improvement of motor symptoms in PD patients, cueing might also have an effect on response inhibition as both automatic repetitive responses and response inhibition are controlled by the basal ganglia. If cueing raises the attention to the task at hand, this could lead to faster selection of the appropriate response. Maybe cueing improves the internal timing, activating and inhibiting the STN on more appropriate times, improving the ability. Or if, in response to cueing, a switch between the basal ganglia and the cerebellar pathways can be demonstrated in healthy subjects, this might have a positive effect on the defective response inhibition ability of PD patients.

This research will be conducted to investigate the influence of both auditory slow cues (0.75 Hz) and fast cues (3 Hz) on the response inhibition ability of healthy subjects compared to an uncued condition. The focus will be on the performance of those subjects, as well as on their cortical electrophysiological response in both the time (ERP) and frequency domains (ERD/ERS). This research will be conducted in order to gain more knowledge about brain networks in response inhibition, and about the influence of cues on these networks. In order to do this, this research will try to find the answers to the following questions:

- What is the effect of cues on the reaction times of the healthy subjects while they are performing a Go/No-Go task?
- What is the effect of cues on the amount of mistakes healthy subjects make during a Go/No-Go task?
- What is the effect of cues on the ERP of healthy subjects in response to both Go and No-Go stimuli received during a Go/No-Go task with respect to N2 and P3 peak amplitude and latency?
- What is the effect of cues on the power of the cortical activation and deactivation of healthy subjects while they are performing a Go/No-Go task?

2 Methods

2.1 Participants

Twenty healthy subjects were recruited to participate in the experiment, which took place at the Donders Center for Neuroscience at the Radboud University in Nijmegen. An overview of the demographic can be found in table 1. The participants were between 19 and 29 years old, with an average age of 23.15 ($\pm$ 2.78) years. Two subjects were left handed, but regularly used their right hand to perform certain tasks. Participants could choose between a measurement in the morning, afternoon or evening, depending on their own schedules and preferences. Five measurements were performed in the morning, eleven in the afternoon and four in the evening. Before the measurement the head circumference of the subject was measured in order to confirm if the EEG cap would fit. The average head circumference was measured to be 57.30 ($\pm$ 1.81) cm. All participants gave written informed consent before the start of the measurement.

Table 1: Participants' demographic (N = 20)

Gender	**N (%)**
Male	8 (45.45)
Female	12 (54.55)
Age	**Years (SD)**
Average	23.15 (2.78)
Handedness	**N (%)**
Right	18 (90)
Left	2 (10)
Head Circumference	**cm (SD)**
Average	57.30 (1.81)

During recruitment, all possible participants received the checklist with exclusion criteria listed below. If at least one of these applied to the participant, they were excluded from the experiment if they:

- had brain or head surgery,
- had a history of substance abuse,
- had skin conditions on the head, e.g. psoriasis or eczema,
- were known to have psychiatric and/or neurological disorders, comparable to epilepsy,
- took medication with visible effects on EEG prior to the experiment, e.g. antidepressants.

2.2 Experimental Design

2.2.1 Participant Preparation

After giving informed consent, the participant was prepared to participate in the experiment. First, the EEG system, i.e. the Waveguard Original EEG cap[70] together with their eego^{TM} amplifier[71], was connected. The EEG was recorded with 1024 samples per second. The cap had 32 gel-electrodes, which were positioned in the 10-10 international layout. Cz was placed exactly in the middle of the head by placing it directly in between the inion and the nasion, but also in between the left en right pre-auricular points. Next, the cap was adjusted until the midline was on the line between the inion and the nasion. Gel was applied to AFz and POz, which were used as ground and reference electrodes. Thereafter, gel was applied to reduce the impedance of the rest of the electrodes below the threshold of 10kΩ. This process took around 30 minutes.

The participant was instructed once more, after which they sat down comfortably at the desk with the experimental laptop. The laptop was placed with the center of its screen approximately 60 cm from the participant's eyes. Both brightness and volume settings were checked to be at 100% and 50% respectively. Next, the ET-1 Insert Earphones of Etymotic[72] were applied and the experiment would begin.

(a) (b) (c)

Figure 5: (a) Go stimulus: grey background with 60% of the screen filled by a green rectangle. (b) Screen with the focus dot. (c) No-Go stimulus: grey background with 60% of the screen filled by a red rectangle.

2.2.2 The Experiment

The experiment consisted of a Go/No-Go task (15 blocks) and a Go Only task (4 blocks). During the Go/No-Go task, the participant was instructed to react as quickly as possible to a Go stimulus (figure 5 (a)) by clicking on the left mouse button with their right hand. If the participant received a No-Go stimulus (figure 5 (c)), they had to withhold this reaction. During the Go Only task, No-Go stimuli were not given. Regarding their response to the Go stimuli, the participant got the same instructions, i.e. click as quickly as possible on the left mouse button with your right hand.

Every block consisted of 40 stimuli. During the blocks of the Go Only task, the participants received 100% Go stimuli, whereas they received 70% Go stimuli and 30% No-Go stimuli during the blocks of the Go/No-Go task. At the beginning of each block there was a baseline period of 10 seconds where no stimuli were presented. The participants were instructed to sit still, watch the focus dot (figure 5 (b)), and wait for the first stimulus to be shown.

The first and second stimuli of each block were always a Go stimulus. However, this was not known to the participant. Each stimulus was presented for 1.5 seconds before disappearing, after which the participant's response was no longer recorded. The stimulus also disappeared after a response of the participant. The next stimulus was shown after a jittered inter-trial interval of 2-3.5 seconds. In between two stimuli, the focus dot was shown to reduce lateral eye movements (figure 5 (b)). Mistakes were registered when the participant failed to react to Go stimuli or when the participant reacted to No-Go stimuli. If the participants responded correctly to Go stimuli, their reaction time to that stimulus was saved.

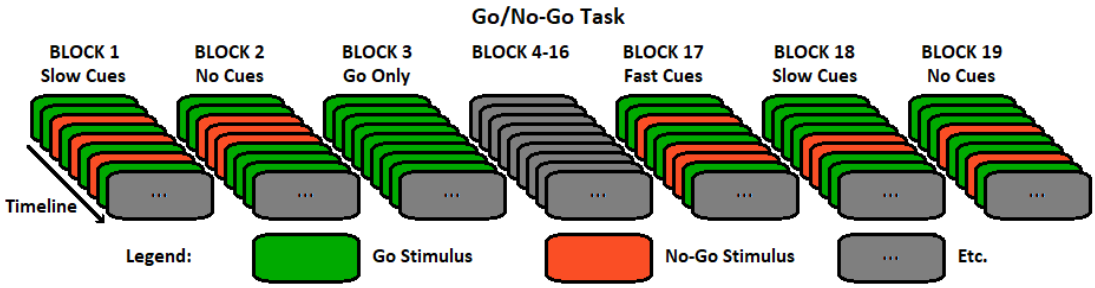


Figure 6: Experimental task design. This example shows 19 blocks, of which 13 are omitted. It can be seen that the first two stimuli for each block were always Go stimuli, whereas the rest of each block contained randomised Go and No-Go stimuli. In this figure, only 8 stimuli are shown per block as the rest is omitted. Omissions were due to the repetitiveness of the table. Each block had a random cueing condition, shown here below the block number.

Each block was assigned one of the following auditory cueing conditions: No Cues, as a control condition, Slow Cues, presented at a frequency of 0.75 Hz, or Fast Cues, presented at a frequency of 3 Hz. The cues were also presented during the baseline period of each block. During the Go-Only task, no cues were presented. For the Go/No-Go task, five of the 15 blocks were assigned No Cues, five were assigned Slow Cues, and the last five were assigned Fast Cues. The sequence of the blocks was randomised, including those of the Go Only task. The cues were on the background only, the subjects were instructed to do nothing in response to the cues. Figure 6 shows a theoretical example of the experiment. This example shows a series of randomised blocks with randomised cueing conditions. It can be seen that the Go Only blocks are included in the randomisation. Taking a break in between blocks was recommended, but optional, except after every fifth block, when the break was obligatory.

Shortly before and after performing the Go/No-Go task, two short questionnaires were filled out. These provide insights on the sleepiness and the concentration of the subject. The Karolinska Sleepiness Scale was used, as well as a modified version to assess the subject's concentration levels (figure 7 (a) and (b)).

2.2.3 Experiment Development

The experiment was created in Matlab, using Psychtoolbox-3[73]. The experiment consisted out of four types of screens, namely instruction screens, Go stimuli, No-Go stimuli, and screens containing a focus dot. The background of these screens was always grey (R:138, G:138, B:138). The instruction screens were shown before the actual task and repeated once more what the participant had to perform. After the instruction screens, during the baseline period, the screen displayed a small, red (R:250, G:78, B:37) focus dot (figure 5 (b)) to reduce the effects of eye movements on the EEG. Both stimuli showed a rectangle in the middle of the screen. The size of the rectangle was 60% of the screen. For the Go stimulus (figure 5 (a)), the rectangle was green (R:0, G:170, B:0). For the No-Go stimulus (figure 5 (c)), the rectangle was red (R:250, G:78, B:37). All colours were chosen so the luminance, measured with the Konica Minolta LS-100[74] at 60 cm from the middle of the screen, was always approximately the same ($\pm$ 46 cd/m^2). The calibration preset was used as well as the setting for peak measurements with absolute values. Equal luminance is important, as this reduced the amplitude of the visual ERP. The cues were created by generating a two sine waves with a frequency of 350 Hz, with the same phase to create stereo sound. The duration per cue was 0.1 seconds, with the first part being used for a linear fade in and the last part as a linear fade out. Both fades had a duration of 0.005 seconds.

Degree of Sleepiness	
1	Extremely alert
2	Very alert
3	Alert
4	Fairly alert
5	Neither alert nor sleepy
6	Some signs of sleepiness
7	Sleepy, no effort to stay awake
8	Sleepy, some effort to stay awake
9	Very sleepy, great effort to stay awake, fighting sleep
10	Extremely sleepy, can't stay awake

(a)

Degree of Concentration	
1	Extremely concentrated
2	Very concentrated
3	Concentrated
4	Fairly concentrated
5	Neither concentrated nor distracted
6	Some signs of distractedness
7	Distracted, no effort to stay focused
8	Distracted, some effort to stay focused
9	Very distracted, great effort to stay focused
10	Extremely distracted, can't stay focused

(b)

Figure 7: (a) The original Karolinska Sleepiness Scale where the subjects indicate their sleepiness on a scale from 1 to 10. (b) The modified scale where the subjects indicate their concentration levels from 1 to 10.

2.3 Data Analysis

2.3.1 Preprocessing

The preprocessing and processing of the EEG data were performed in Matlab using an open-source toolbox named EEGlab[75]. After loading the EEG data, it was rereferenced to the grand average of all electrodes. The acceleration channels were then removed from the data. Also, the data in between blocks, when the participants were taking breaks, was removed. Next, the data was filtered with a second order non-causal bandpass Butterworth filter with cutoff frequencies at 1 and 95 Hz (figure 8). 50 Hz line noise was removed with a second order non-causal bandstop Butterworth filter with cutoff frequencies at 48 and 52 Hz. Last, bad channels were removed if their amplitude was lower than 1 mV or if the upper threshold was exceeded. The upper threshold was determined by the mean amplitude and twice the standard deviation of all electrodes. Thereafter, the data was visually inspected in order to find and remove noisy channels.

In order to remove eye blink artefacts, as well as horizontal eye movements, the electrocardiogram (ECG) and muscle artefacts, an independent component analysis (ICA) was performed. After extracting the independent components, they were visually inspected. Components that showed peaks throughout the whole data, showed high power centered around the prefrontal electrodes and had power spectra where no peaks were found in physiological frequency bands (i.e. alpha and beta) were removed from the data. Components with typical ECG time courses and topographies were also removed. For the removal of muscle artefacts, often originating from the neck and jaw muscles, temporal components with peaks in the gamma band, but no peaks in other physiological frequency bands, were removed.

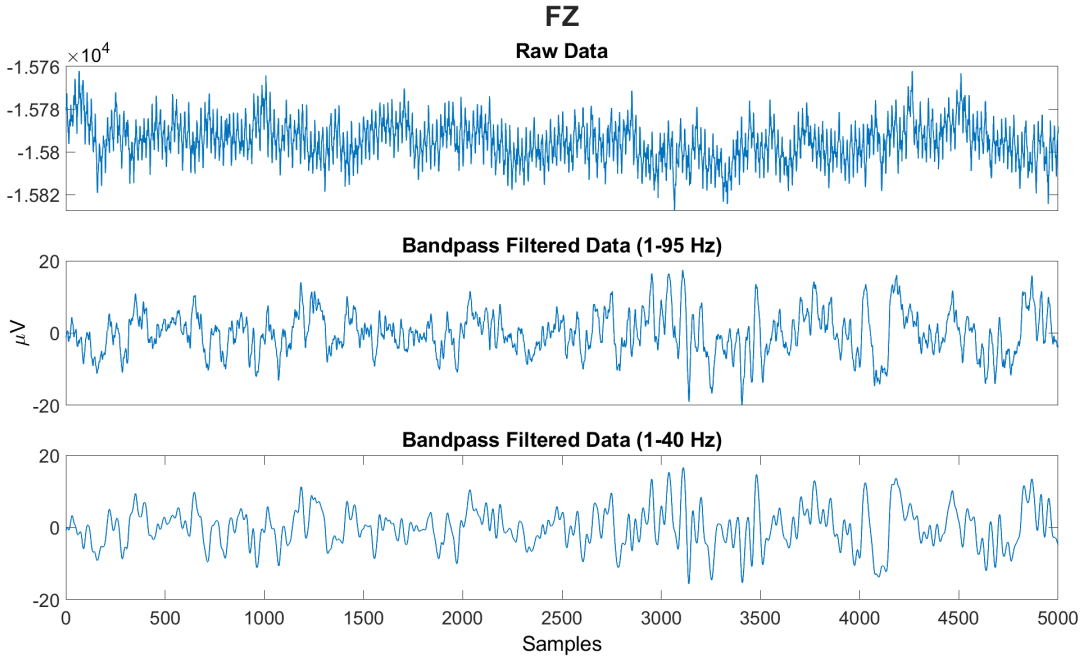


Figure 8: Three times the same 5000 samples of EEG data of the Fz electrode. The raw data is on top, the preprocessed (bandpass filter between 1 and 95 Hz) data that was used for the ERD/ERS in the middle. On the bottom the bandpass filtered (between 1 and 40 Hz) EEG data that was used for the ERP.

2.3.2 Processing

Behavioural Data During the experiment, the reaction times of the participants were recorded. Matlab recorded when a stimulus was presented and when the participant pressed the left mouse button. To investigate the accuracy, the amount of mistakes the participants made were recorded. There was a counter that increased for every missed Go stimulus and for every response to a No-Go stimulus. The results were categorised into four groups, based on the four conditions present in the experiment; No Cues, Slow Cues, Fast Cues and Go-Only. Go-Only was included to be a baseline for the other conditions. The results were plotted in bar graphs for visualisation. The coefficient of variation was then studied to see if cues may have an effect on the inter-individual variability for the reaction times and for the amount of mistakes.

ERP In order to produce the ERP of the participants, the preprocessed data was filtered a second time, now with a second order non-causal low-pass Butterworth filter with a cutoff frequency of 40 Hz (8). Thereafter, the trials were extracted from Go/No-Go task blocks. Each trial consisted out of $1\frac{1}{4}$ seconds, starting 250 milliseconds before stimulus presentation and ending 1 second after. All trials were then split up based on the cueing conditions. For each cueing condition, trials were categorised based on stimulus type. The average of all trials was calculated for the F_1, F_z, and F_2, as well as the C_3, C_z, and C_4 electrodes. This was then averaged, what resulted in the ERP for each subject. Only these electrodes were included because both N2 and P3 peaks were expected to be found in the frontal and central electrodes closest to the midline.[61]

For the ERP of each subject, the N2 and P3 peaks were then found. The N2 peak was found by looking for local minima between 240 milliseconds and 320 milliseconds after stimulus onset. From those, the minimal value was selected to be the N2 peak. Both the amplitude and latency of the peaks were stored, in order to analyse whether cueing had an effect on the strength of response inhibition and if cueing had an effect on the internal timing mechanism of the participants. This was then repeated for the P3 peaks by finding the maximal value between 320 milliseconds and 500 milliseconds after stimulus onset. With the purpose of visualisation, both the average ERP of all participants in response to Go stimuli and the average ERP in response to No-Go stimuli were plotted in one figure per cueing condition.

ERD/ERS For the analysis of the ERD/ERS, first the trials were extracted from the original preprocessed data. A trial originated from Go/No-Go task blocks and consisted of one second of data, starting from the stimulus presentation. The trials were divided based on their stimulus type (Go or No-Go) and their cueing condition (No Cues, Slow Cues or Fast Cues). Next, the power spectrum of each trial was calculated with Welch's Method. Therefore each trial was divided into eight segments with 50% overlap. Each segment was windowed with a hamming window. The frequencies were zero padded to a total of 5120 and the sampling frequency was 1024. If the average power of a trial was found to be larger than the sum of the average power of all trials of their condition and two times the standard deviation, the trial was excluded. The power of all remaining trials of each condition was averaged in order to find P_{trials} of equation 1.

$$ERD/ERS = \frac{P_{trials} - P_{baseline}}{P_{baseline}} \tag{1}$$

Next, the baselines were extracted from the baseline periods of all the blocks. There were five blocks per cueing condition, so the three conditions were filled with five baselines each. The first 3 seconds of the baseline periods were excluded, because participants might still have been moving then. Also the last second was excluded, because the participants might have been fully prepared on clicking when the first stimulus arrives. Therefore, each baseline consisted of six seconds. The power of the baselines was then calculated with Welch's Method with the same setting as for the trials. None of the baselines were excluded,

so the power of all baselines was averaged in order to find $P_{baseline}$.

The ERD/ERS of each group was calculated with equation 1, using both P_{trials} and $P_{baseline}$. This means that $P_{baseline}$ of the, for instance, No Cues condition was subtracted from P_{trials} of the Go stimuli of the No Cues condition, to be divided by $P_{baseline}$ of the No Cues condition. This was repeated for the Slow Cues condition and the Fast Cues condition and then done as well for the No-Go stimuli. The ERD/ERS of the No Cues condition was subtracted from both the other conditions, to see the effects of slow versus fast cues with respect to no cues. The results were split up into four frequency bands: the theta (4-8 Hz), alpha (8-13 Hz), beta (13-30 Hz), and lower gamma band (30-45 Hz). Topoplots were used to visualise the results.

2.3.3 Statistical Analysis

A within subject analysis was performed. Therefore, in the case of two related groups, the parametric test was the dependent t-test, whereas the non-parametric test was the Wilcoxon signed rank test. In the case of more than two related groups, the parametric test was the ANOVA with repeated measures and the non-parametric test was the Friedman test. The ANOVA with repeated measures works under the assumption of normality and sphericity of the data. Hence, the data was always tested on normality first with the Kolmogorov-Smirnov (KS) test. If normality could be assumed, a Mauchly test was conducted when needed in order to prove sphericity. If both criteria were met, the parametric test was conducted to test the data. If not, the non-parametric test was conducted. For each test, the significance level was 0.05 and the Bonferonni-Holm method was used to control family-wise error rate.

Behavioural Data First, the reaction times and the amount of mistakes of the participants were analysed. For both outcome measures, there were four dependent groups that needed to be compared; No Cues, Slow Cues, Fast Cues, and Go Only. This indicated that either a repeated measures ANOVA or a Friedman test should be conducted. This depended on the normality of the data. First, the data was split up into four subcategories, being the same as the four dependent groups from before. Next, normality was tested for each of the subgroups with the KS test. If all subgroups were normally distributed, they were tested on sphericity with the Mauchly test. In the case both criteria were met, the repeated measures ANOVA was conducted, if not, the Friedman test. After this, a posthoc analysis was performed in order to test for differences between each group (i.e. the difference between No Cues and Slow Cues, No Cues and Fast Cues, and No Cues and Go Only, etc.).

ERP Both N2 and P2 peak amplitude and N2 and P3 peak latency in response to No-Go stimuli were compared between cueing conditions. Both outcome measures had three related groups, so either a repeated measures ANOVA or a Friedman test should be used. The groups were tested on normality and sphericity again if needed and afterwards a posthoc analysis was performed test for differences between each group.

Next, the ERP data was used to show that the Go/No-go task was effective for all conditions in all participants. Therefore, for each condition, the N2 and P3 peak amplitudes in response to Go stimuli were tested against the N2 and P3 peak amplitudes in response to No-Go stimuli. This analysis had only two dependent variables, so either a dependent t-test or a Wilcoxon signed rank test was conducted in order to test for these differences. This depended on normality. Rather than testing for normality for each of the two related variables, only the difference between them needed to be tested with the KS test.

ERD/ERS To analyse the ERD/ERS data, the previously obtained results were split up in 16 zones (table 2), each containing a certain amount of electrodes. The zones were as follows: frontal (F), fronto-central (FC), temporal (T), central (C), parietal (P) and occipital (O). The electrodes then were divided into one of three groups based on their location. If they were located on the left side of the midline, they were shared under the left group (L) and if they were located on the right side, under the right group (R). If a zone had an electrode located on the midline, that electrode was put in the central group (ctr). The final division can be seen in table 2.

It is hypothesised that when the cerebellar pathways become active, so do the premotor cortex and the parietal cortex. The premotor cortex is measured by the FC electrodes, whereas the parietal cortex is measured by the P electrodes. Those zones are therefore possibly associated with the activation of the cerebellum. The zones associated with the activation of the basal ganglia were F, for the prefrontal and frontal cortices, partly FC for the supplementary motor cortex, and C for the somatosensory motor cortex. So the temporal and occipital electrodes are not necessary for measuring response inhibition, but they might provide insight in the responses of the auditory and visual cortices.

Table 2: Overview of which electrodes are found in which zone and which zone is in associated with which pathway (either the basal ganglia (BG) or the cerebellum (C))

Zone		Electrodes			Pathway
F	L	Fp_1	F_3	F_7	BG
	ctr	Fp_z	F_z		
	R	Fp_2	F_4	F_8	
FC	L	FC_1	FC_5		C/(BG)
	R	FC_2	FC_6		
C	L	C_3	CP_1	CP_5	BG
	ctr	C_z			
	R	C_4	CP_2	CP_6	
T	L	T_7			
	R	T_8			
P	L	P_3	P_7		C
	ctr	P_z			
	R	P_4	P_8		
O	L	O_1			
	ctr	PO_z	O_z		
	R	O_2			

The ERD/ERS data consisted of two dependent groups. The first group consisted out of data of the No Cues condition subtracted from the Slow Cues condition. The second group consisted of data of the No Cues condition subtracted from the Fast Cues condition. The groups were tested for normality and if that criterion was met, a dependent t-test or a Wilcoxon signed rank test was conducted in order to test these groups for differences. Due to the Bonferonni-Holm method, which corrects for the amount of tests that were conducted (in this case 64, as 16 zones and 4 frequency bands for each zone were compared), the smallest found p-value was compared to a significance level of $\frac{0.05}{64} = 7.8e^{-4}$. A posthoc analysis was conducted if differences were found initially.

3 Results

Data analysis was performed on the data of 19 participants, as one of them was excluded due to falling asleep during the experiment. First, the data was analysed on behavioural level, before analysing the EEG data in the time (ERP) and frequency domains (ERD/ERS).

3.1 Behavioural Data

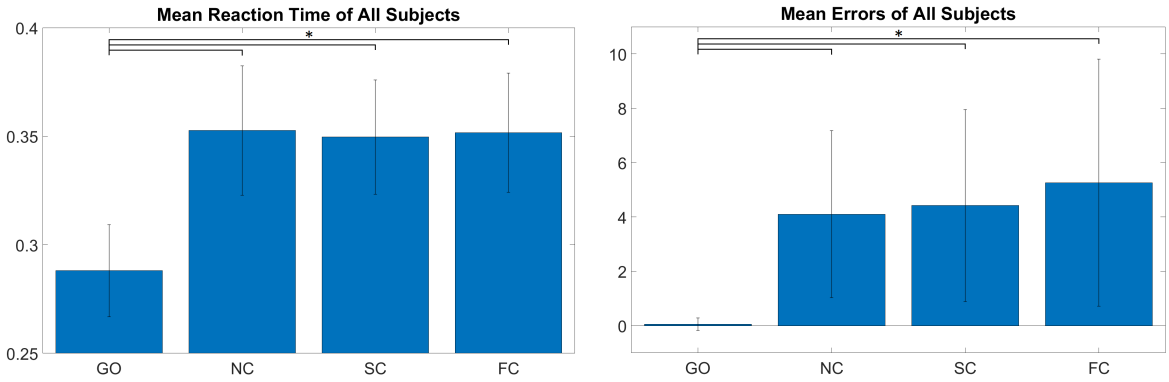
Figure 9a shows the average reaction times of all subjects with the standard deviation. A Friedman's test showed a significant difference ($p = 1.45e^{-7}$) in reaction time. The results of the post-hoc analysis (table 3) show significant differences between the Go Only condition and every other condition. However, no significant differences were found between cueing conditions. The coefficients of variation for the reaction times were found to be 7.4% for GO, 8.5% for NC, 7.5% for SC, and 7.8% for FC.

For the amount of mistakes the participants made (figure 9b), a Friedman's test also found a significant difference between the conditions (p-value of $1.17e^{-7}$). In the posthoc analysis, no significant differences between cueing conditions were found, as only the Go Only condition was significantly different from the rest (table 3). For the amount of mistakes, the coefficients of variation were found to be 435.9% for GO, 74.8% for NC, 79.9% for SC, and 86.3% for FC.

Table 3: P-values found in the post-hoc analysis of the reaction times (left) and error rates (right).

Reaction Times						
Condition 1	GO	GO	GO	NC	NC	SC
Condition 2	NC	SC	FC	SC	FC	FC
P-values	$1.3e^{-4}$	$1.3e^{-4}$	$1.3e^{-4}$	.421	.687	.184

Error Rates						
Condition 1	GO	GO	GO	NC	NC	SC
Condition 2	NC	SC	FC	SC	FC	FC
P-values	$1.2e^{-4}$	$1.8e^{-4}$	$2.9e^{-4}$	.630	.078	.136



(a) *(b)*

Figure 9: (a) The average reaction times ± the standard deviation of all subjects for each condition. In order from left to right: Go-Only (GO), No Cues (NC), Slow Cues (SC), and Fast Cues (FC). (b) The average amount of mistakes of all subjects for each condition ± the standard deviation. The categories from left to right are the same, i.e. GO, NC, SC, and FC.

3.2 ERP

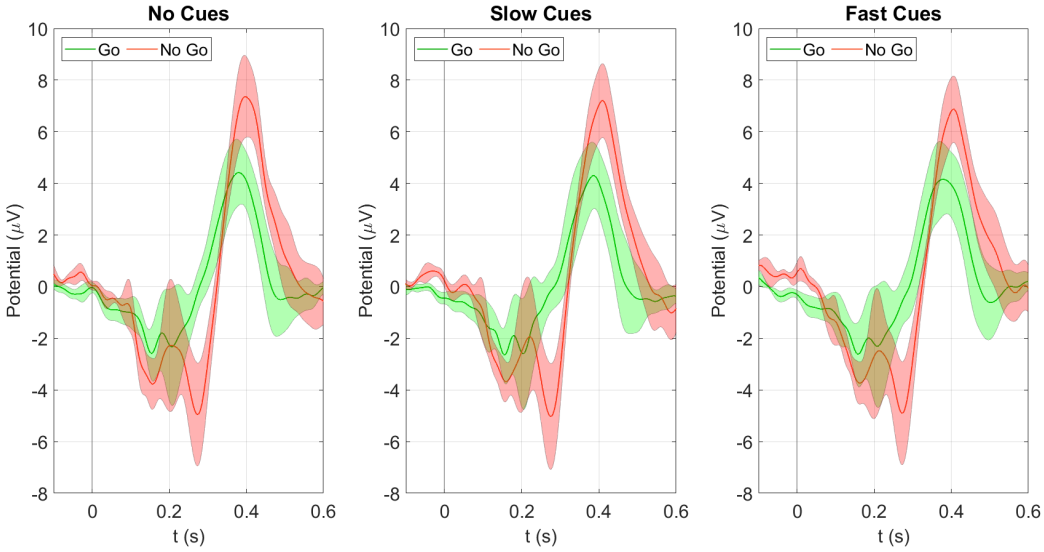


Figure 10: The ERP plots for the No Cues (left), Slow Cues (middle), and Fast Cues (right) groups. At t=0, either a Go or a No-Go stimulus was presented. The green graph shows the average response to Go stimuli with 95% confidence intervals. The red graph shows the average response with 95% confidence intervals to No-Go stimuli.

The average ERPs of all subjects were plotted with 95% confidence intervals for the No Cues condition (figure 10 (left)), Slow Cues condition (figure 10 (middle)), and the Fast Cues condition (figure 10 (right)). First, it was tested whether or not the Go/No-Go task worked as expected. A Wilcoxon signed rank test was conducted to test if the N2 and P3 peak amplitude of the No-Go graphs was higher than the N2 and P3 peak amplitude of the Go graphs. The p-values can be seen in table 4. When compared to the Bonferroni-Holm corrected significance level of $\frac{0.05}{6} = 8.3e^{-3}$, it can be seen that both N2 and P3 peak amplitudes were significantly different between Go and No-Go groups.

Table 4: P-values found for differences between N2 and P3 peak height of the Go and No-Go groups.

Condition	N2 Peaks	P3 Peaks
No Cues	0.0028	0.0006
Slow Cues	0.0002	0.0004
Fast Cues	0.0022	0.0040

Next, a Friedman's test was conducted in order to compare the N2 and P3 peak amplitude and latency between conditions. When comparing the p-values (table 5) to the significance level of $\frac{0.05}{4} = 1.3e^{-2}$, it can be seen that no significant differences were found between conditions for N2 and P3 peak amplitude and latency. This indicates that no posthoc analysis was necessary.

Table 5: P-values found with Friedman's test for differences between conditions in N2 peak height and timing and P3 peak height and timing.

	N2 Peak		P3 Peak	
	Amplitude	**Latency**	**Amplitude**	**Latency**
p-value	0.8607	0.8607	0.4493	0.5488

3.3 ERD/ERS

The ERD/ERS for each cueing condition was calculated for each frequency band. Then the No Cues condition was subtracted from both the Slow Cues condition and the Fast Cues condition for each frequency band for both Go and No-Go responses. The results were plotted in figures 11-14.

For the theta band (4 - 8 Hz), it can be seen that in response to Go stimuli, for both conditions, there is more activation in the fronto-central regions of the brain, compared to the No Cues condition (figure 11). This ERD seems to be deeper for the Slow Cues than for the Fast Cues condition. Also, for both conditions, it can be seen that in response to No-Go stimuli, this area was spread more widely. In all subplots, there is more activation (ERS) of varying strengths directly posterior to the fronto-central through, with the Fast Cues condition being more positive overall. Directly after the positive peaks in the parietal and visual areas, there is again an ERD. In the Fast Cues condition in response to Go stimuli, there is a large activation at the location of the T7 electrode.

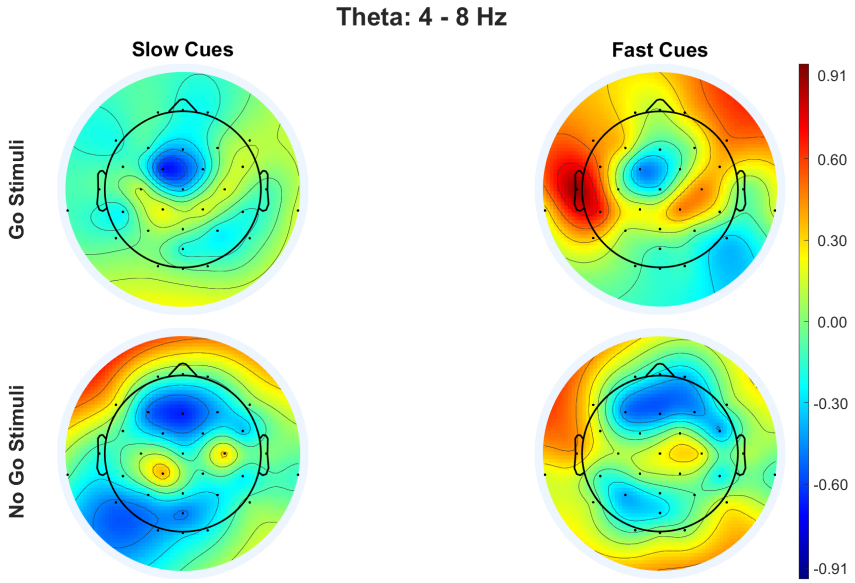


Figure 11: Four topoplots of ERD/ERS data in the frequency band theta (4-8 Hz). The responses to Go stimuli are shown in the top row, while the responses to No-Go stimuli are shown in the bottom row. The first column contains the responses to Slow Cues - No Cues and the second column to Fast Cues - No Cues. The scale goes from 0.91 (ERS) to -0.91 (ERD).

A KS test showed that the values in the theta band were not normally distributed. Therefore the non-parametrical Wilcoxon signed rank test was performed for each of the zones found in table 2. None of the found p-values (table 6) was smaller than the Bonferonni-Holm corrected significance level of $7.8e^{-4}$, so no significant differences were found between the slow and fast cueing conditions.

Table 6: P-values found for each zone in both Go and No Go groups for the theta band.

Zone	F			FC		C			T		P			O		
	L	ctr	R	L	R	L	ctr	R	L	R	L	ctr	R	L	ctr	R
Go	.983	.648	.617	.523	.795	.913	.711	.948	.758	.446	.723	.711	.094	.528	.679	.372
No-Go	.777	.648	.648	.435	.463	.309	.306	.498	.619	.981	.906	.372	.327	.679	.446	.948

For the alpha band (8 - 13 Hz), plotted in figure 12, in response to the Go stimuli there seems to be a pattern, with focal zones in the center of the frontal areas and to the sides in the left and right parietal areas. In the right parietal area there is an ERS, while an ERD can be found on the left side. The response to the Fast Cues seems to be stronger overall. In response to the No-Go stimuli, the left parietal zone exhibits a larger ERD than in the Go situation. Besides, the more rostral areas seem to be involved as well. The right parietal zone now shows an ERD, which is even stronger for the Fast Cues condition. The frontal ERS seems to have disappeared for the No-Go situation.

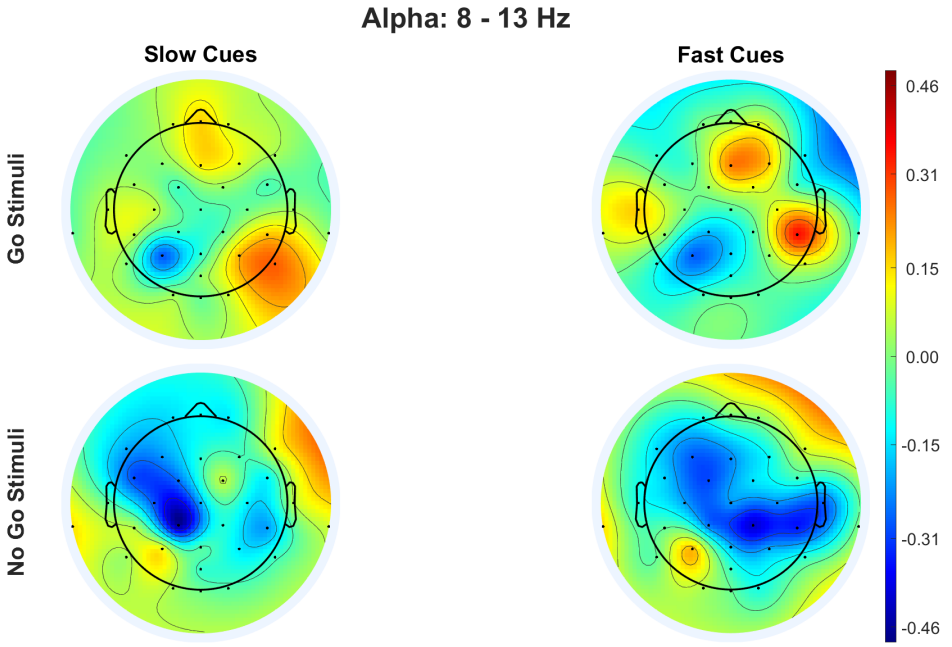


Figure 12: Four topoplots of ERD/ERS data in the frequency band alpha (8-13 Hz). The responses to Go stimuli are shown in the top row, while the responses to No-Go stimuli are shown in the bottom row. The first column contains the responses to Slow Cues - No Cues and the second column to Fast Cues - No Cues. The scale goes from 0.46 (ERS) to -0.46 (ERD).

For the alpha band, the KS test also found that the data was not normally distributed. The same tests were performed as for the theta band. The p-values can be found in table 7. Again, no significant differences were found between subjects.

Table 7: P-values found for each zone in both Go and No Go groups for the alpha band.

Zone	F			FC		C			T		P			O		
	L	ctr	R	L	R	L	ctr	R	L	R	L	ctr	R	L	ctr	R
Go	.913	.396	.500	.758	.586	.586	.845	.349	.407	.085	.381	.811	.472	.744	.777	.215
No-Go	.983	.372	.349	.554	.381	.758	.420	.744	.332	.102	.943	.679	.679	.396	.679	.472

When looking at the topoplots of the beta (13 - 30 Hz) frequencies (figure 13), what directly stands out are the synchronisations around T7 and T8, especially on response to Slow Cues. In comparison, the desynchronisations in response to Go stimuli in both conditions in the fronto-central region are very small. The left side seems to have a more synchronous pattern than the right side in both the Slow Cues and the Fast Cues condition. Especially in the right centro-parietal area of the No-Go situation, as a large ERS can be seen there. The responses to Fast Cues seem to have a smaller amplitude overall than the responses to Slow Cues.

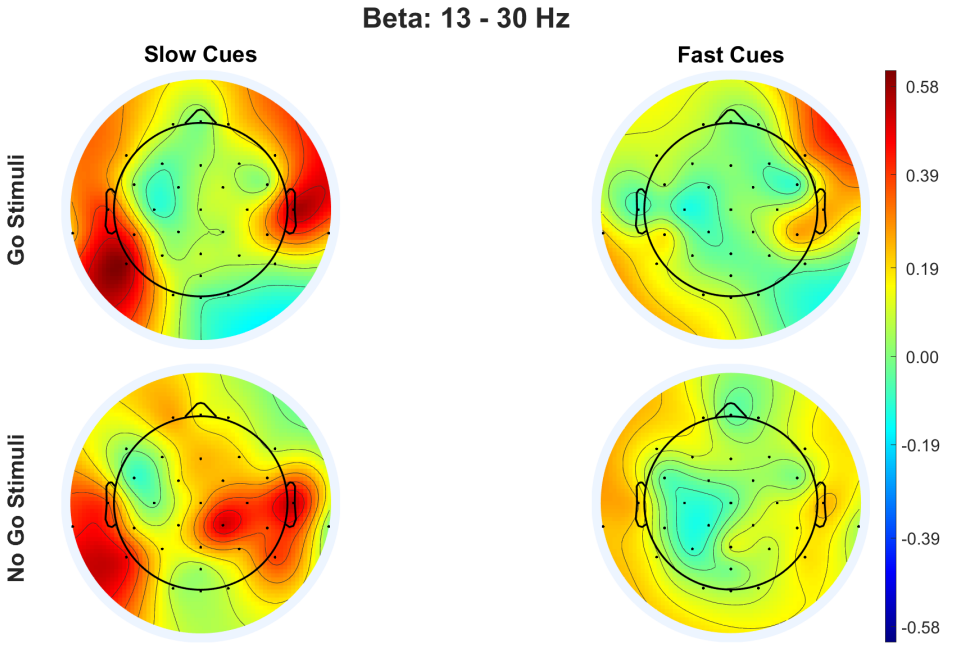


Figure 13: Four topoplots of ERD/ERS data in the frequency band beta (13-30 Hz). The responses to Go stimuli are shown in the top row, while the responses to No-Go stimuli are shown in the bottom row. The first column contains the responses to Slow Cues - No Cues and the second column to Fast Cues - No Cues. The scale goes from 0.58 (ERS) to -0.58 (ERD).

The data of the beta band was also found to be not normally distributed. Again, a Wilcoxon signed rank test was performed and none of the results are significantly different between subjects (p-values in table 8).

Table 8: P-values found for each zone in both Go and No Go groups for the beta band.

Zone	F			FC		C			T		P			O		
	L	ctr	R	L	R	L	ctr	R	L	R	L	ctr	R	L	ctr	R
Go	.231	.420	.064	.227	.227	.020	.058	.133	.246	.845	.028	.022	.053	.071	.048	.071
No-Go	.845	.231	.446	.287	.113	.554	.020	.048	.044	.287	.035	.058	.199	.231	.170	.267

For the gamma frequencies (30 - 45 Hz) (figure 14, the patterns found in figure 13 almost repeat themselves, but stronger. High peaks around T7 and T8, compared to those peaks, a small ERD that can be found in the left (fronto-)central regions of all subplots. The right side shows a small ERS. The scales show that the responses in the gamma frequency are the strongest overall.

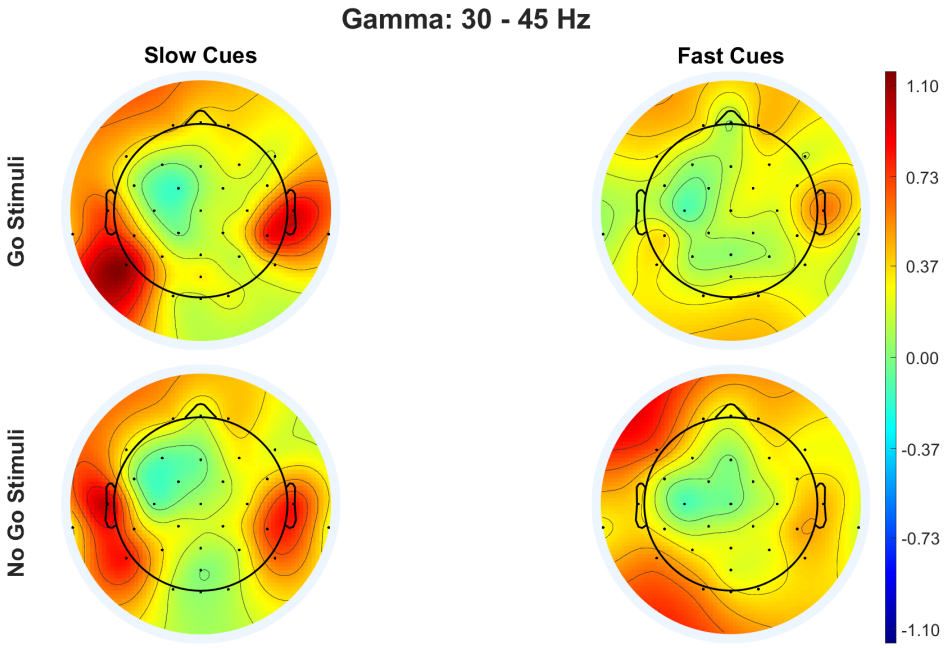


Figure 14: Four topoplots of ERD/ERS data in the frequency band gamma (30-45 Hz). The responses to Go stimuli are shown in the top row, while the responses to No-Go stimuli are shown in the bottom row. The first column contains the responses to Slow Cues - No Cues and the second column to Fast Cues - No Cues. The scale goes from 1.10 (ERS) to -1.10 (ERD).

The KS test found the data in the gamma band to be not normally distributed. Therefore, once more for each zone, a Wilcoxon signed rank test was performed. There were no significant differences found between subjects (p-values can be found in table 9).

Table 9: P-values found for each zone in both Go and No Go groups for the gamma band.

Zone	F			FC		C			T		P			O		
	L	ctr	R	L	R	L	ctr	R	L	R	L	ctr	R	L	ctr	R
Go	.025	.018	.007	.102	.028	.043	.058	.035	.102	.249	.163	.102	.157	.528	.215	.679
No-Go	.648	.528	.215	.381	.177	.795	.349	.349	.246	.586	.653	.349	.500	.528	.777	.372

4 Discussion

4.1 Behavioural Data

This experiment was conducted to investigate the influence of auditory cues on the response inhibition ability of healthy subjects. First, the effects of cues on the performance of healthy subjects on a Go/No-Go task was analysed by comparing the reaction times and amount of mistakes of the participants for each cueing condition. The results show that between cueing conditions there were no significant differences in reaction times and amount of mistakes made. If the cerebellar pathway had taken over in any of the cueing conditions, it was expected that the reaction times would be slower for that situation, as reacting with a pre-potent response via the basal ganglia normally is the faster method.[10,41] However, healthy participants were included, so it could be that we merely do not see the effects of the cerebellar pathway taking over, since the basal ganglia are not defective. The extrapyramidal system is indeed still active in healthy participants, so the participants were able to respond normally, i.e. quickly, in every situation. The results might be interpreted in a way that, while the cerebellar pathway might become active as well, it does not suppress the extrapyramidal system, provided that it is still working.

If cueing influenced the internal timing mechanisms, given they were pathological, it would be a possibility that responses might be tied to the cue. As the experiment was set up to record responses to the Go and No-Go stimuli, it is not entirely possible to analyse the latency of the cues as they were not recorded. However, the coefficients of variance indicate that there is only a low (around 7-8%) variability with respect to the mean of the data for each cueing condition. During the Slow Cues condition, cues were presented with a frequency of 0.75 Hz. As the responses of the participants were only recorded for 1 second after stimulus onset, this means that there would on average only be 1 cue present anywhere during the trial. If the responses were tied to the cue, this would mean that a large variability was expected during the Slow Cues condition. For the Fast Condition (3 Hz), on average there should be almost 3 cues in every trial. Then the variability should be much lower, as the cue comes on average much earlier in the trial. The coefficients of variation, however, are quite similar for both conditions, which therefore indicates that in the healthy situation, responses are not necessarily tied to the cues.

Response inhibition is a task that requires attention and goal-directed behaviour.[76] If cueing improves attention, that would mean that the task at hand would be performed better with less mistakes. Although the results indicate that there is no significant difference between cueing conditions for the amount of mistakes, a small trend can be seen in figure 9. The trend shows that with faster cues, more mistakes are made. This could indicate that, especially faster, cues could be perceived as distracting by most people, as the coefficient of variation shows that the variability between subjects is largest for the fastest cues.

Figure 9 shows that the average reaction times for the Go Only task were significantly shorter than the reaction times for the Go/No-Go task, regardless the cueing condition. This was conform the expectations, as the Go Only task can be compared to a simple reaction time test, whereas the Go/No-Go task is commonly used as a more complex variant. Previous research has shown that the reaction times during simple reaction time tests are quicker than during a Go/No-Go task.[77] Both the Go Only and Go/No-Go task require the same movements, so the difference can be explained by the fact that there are no negative consequences related with the Go Only task, which allows the participants to respond without assessing the situation. Besides, it could be that during the Go/No-Go task response inhibition is already in effect in order to maintain high motor preparedness.[42,78] Only after stimulus assessment and finding that a Go stimulus has been presented, response inhibition is released and an action can be performed.

4.2 ERP

Considering the ERP data, for all conditions, significant differences were found between N2 an P3 peak amplitudes for the Go and No-Go condition. This indicates that the Go/No-Go task has worked as predicted. No differences were found however, when the conditions were compared to each other. As the N2 peak amplitude in response to No-Go stimuli is associated with the strength of response inhibition [55,61–63], this indicates that the different cueing conditions do not improve or worsen the response inhibition ability of healthy subjects.

Previous research has shown that patients with cerebellar lesions showed longer N2 and P3 peak latency. [79] This indicates that the cerebellum normally has, in some degree, influence on the response inhibition ability of people. However, it agrees with the cerebellum not actually taking over the role of the basal ganglia in response inhibition tasks when stimulated with Slow Cues, but having more of a supporting role. Therefore, it is logical that for all conditions the N2 and P3 peak latency remained the same in healthy subjects.

Receiving a external cue during the Go/No-Go task could also be considered dual tasking, as the participant receives additional input in the form of a cue. This could improve the attention to the task at hand, but processing the external cue could also take up some of the available mental capacity. Processing more cues would then take up more capacity, decreasing the ability to respond as fast as possible. Considering that in PD, the cognitive load of performing one task is often already too much, this could mean that presenting too high frequency cues might have a negative effect. [9] In this experiment, that would mean that the Fast Cues condition increases the cognitive load so much, that their results (N2 and P3 peak amplitude and latency) would suffer. In healthy participants, no significant differences were found, indicating that they had enough mental capacity to receive and process cues while performing the Go/No-Go task.

The N2 peak requires attention to relevant stimulus features [80]. No significant differences were found in the N2 peaks between conditions. This indicates that the different cueing conditions do not improve attention to the stimulus. However, it does not necessarily mean that the cueing conditions do not have any effect on attention. There are two parts of the auditory ERP that could reflect attention; the N1-P2 wave is a sign of early attention [81–83] and the N3 peak might indicate enhanced attention, as it becomes elicited after surprising, interesting, and important stimuli. [82,83] The ERPs collected in this study were not auditory ERPs, so it was not possible to check this hypothesis.

4.3 ERD/ERS

It is important to note that figures 11-14 do not show the average response in frequency domain to Go and No-Go stimuli under different cueing conditions. They show which areas show ERD/ERS when compared to the uncued, control condition. In the theta band, there seems to be an ERD in the fronto-central region, indicating higher power for the No Cues condition than for the Slow Cues and Fast Cues condition. Higher power in this region is associated with worse response inhibition, as this is the location of the supplementary motor area [10,65]. Therefore, it appears that Slow Cues and Fast Cues both might have a positive effect on the response inhibition ability of healthy subjects.

Generally, brain regions activated during a task will exhibit an ERD in the alpha band, whereas regions that are irrelevant and potentially interfering during the task will exhibit ERS in the alpha band [84]. For the Go response, this indicates that the motor regions of the brain are equally active during all cueing conditions, as there is neither an ERD nor an ERS when compared with the control condition. This is highly likely, as only the index finger of the right hand was moved during all conditions.

In figure 13, two large synchronisations can be seen in the areas of the neck and jaw under the influence of Slow Cues. These synchronisations might be muscle artefacts. Although an ICA was performed to remove those, they still might be present in the signal. This is due to the fact that the components found during the

ICA were not purely physiological signals, but also contained small parts of the muscle artefacts. Therefore, during the rejection of the components, a trade-off has to be made between rejecting all muscle artefacts and retaining most of the physiological signal. Due to this fact, it is hard to say something interesting about the beta band in response to cueing with Slow Cues. It can be seen that for the Slow Cues there might be response in the centro-parietal regions of the No-Go plot. This however, might also be an effect of the artefacts. On the other hand, those ERS peaks are not necessarily artefacts, as they are not present in response to the Fast Cues condition. This could be explained by the fact that the Fast Cues were better for the attention, decreasing the amount of movements of the participants, or it could be that the cues are processed differently. The beta band is associated with processing sensory information and it could be entirely possible that Slow Cues are processed as separate cues, each with its own response, whereas the Fast Cues might be processed as continuous, with a minimal amount of responses.[47–50] It was also shown before that the beta power decreased in response to Go stimuli, whereas this decrease was terminated early in response to No-Go stimuli . This could explain the stronger responses to No-Go stimuli, than to Go stimuli (overall, the plots in response to No-Go stimuli are more positive than in response to Go stimuli, for both conditions).

In figure 14, the synchronisations that might be muscle artefacts can also be found. In response to the Fast Cues condition, the whole plot seems to show ERS for the response to both Go and No-Go stimuli. The task might be perceived as more dynamic under the influence of Fast Cues than under the influence of No Cues. The response to the No-Go condition is associated with response inhibition, and the responses to Go and No-Go stimuli both show ERS with similar pattern, therefore it is possible that the gamma band does not show effects on response inhibition. This seems to agree with previous research.[69]

4.4 Limitations and Recommendations

This study did not find any significant differences between cueing conditions. This might have to do with the fact that the participant population was healthy. For instance, deviations in the N2 and P3 peak amplitude and latency in the ERP would normally indicate dysfunctional response inhibition[58], which the healthy subjects did not suffer. Besides, the fact that the basal ganglia of healthy participants might not be bypassed by the cerebellar pathways due to cueing, did not only cause us not to see differences in their reaction times. It may also be that it is impossible to see activation of only the cortical areas associated with the cerebellum as also the cortical areas associated with the basal ganglia are active. I would recommend using this experiment to measure response inhibition in PD patients. This might provide more conclusive results.

That there might still be artefacts in the data brings up another point. Although it is hard to fully remove all muscle artefacts without also deleting some physiological data, it is possible to be more selective in inclusion of trials. This is possible because the Go/No-Go task is shown to be effective as the ERPs look good and as expected. Therefore the amount of trials was enough. If in future research this dataset is used again, I would propose that trials with high gamma power are removed from the data as well, instead of only trials with too high power overall. This might have a positive effect on the data quality, so the ERD/ERS data can be regarded for every frequency band.

With this dataset it could be interesting to look to the spectrograms of the data, instead of the ERD/ERS in topoplots alone. In this research, the large time frame per trial caused the plots to be very average and as a results of this, physiological ERD or ERS at certain locations could not be found (e.g. the beta peak in the IFG at the initiation of response inhibition). This could mean that cues still have some effects on the response inhibition ability of healthy subjects, but that we could not see them.

Another thing to make a distinction between are successful and unsuccessful inhibitions. Unsuccessful inhibitions are initiated motor responses that are eventually withheld. This means that participants could start to click the left mouse button, but stop early enough for the computer not to register the click. In

this study, no distinction was made, so there is no way to know how much successful responses eventually made up the ERP of the participants or the correct amount of mistakes that they made. In future studies, I would recommend using accelerometers or EMG data to gain more insight in movements made in response to No-Go stimuli.

Another interesting addition would be a subanalysis where distinction was made between preferences regarding the cueing condition. One participant could have felt more focused without any cues present, while another might have felt more awake and alert with them. This might have influence on their reaction times or amount of mistakes. During our research we asked the participants which condition they preferred, but we did not physically record their answers. I would recommend to do so in future research.

4.5 Conclusion

What are the effects of cues on healthy participants performing a Go/No-Go task? On healthy participants cueing did not have any effects. However, there is reason to believe that cueing might still be effective for improving the response inhibition ability of PD patients. The reaction times and ERP of the participants in this study have shown that the cerebellum did not necessarily take over the response inhibition function of the extrapyramidal system, as no differences were found between cueing conditions. This could indicate that the cerebellum has more of a supporting role for response inhibition. As the extrapyramidal system is defective in PD patients, this could mean that cueing could provide a way that the supporting role becomes leading. Therefore cueing could improve the response inhibition function of PD patients, helping them with all sorts of problems, from their risk-taking behaviour, to their incapability to withhold pre-potent responses. One thing is certain, more research is needed on this subject, especially in PD patients.

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