Evidence of an exogenous input to Superior Colliculus (SC) as a source of saccadic inhibition.

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Introduction

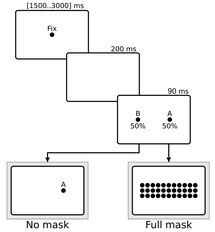
Saccadic inhibition refers to the temporary decrease in saccadic initiation observed when a visual mask appears shortly after the onset of a saccadic target. It has been proposed that the inhibition phenomenon results from a competition between the target and the distractor in visuomotor maps (Reingold & Stampe, 2002, 2004; Guillaume 2012). Interestingly, in addition to these modulations of latency distributions (decrease of probability density by 50%), saccadic inhibition was accompanied by marginal and complex amplitude changes of saccade metric (decrease of saccadic gain by about 10%). These distinct effects on timing initiation and saccade metrics question the uniqueness of the source of perturbation arising within a single visuo-motor map such as the superior colliculus (SC).
In addition, to the best of our knowledge, masking inhibition has only been studied through saccadic responses in the context of oculomotor tasks, implying that it is a visual-only mechanism.
Here, to gain a better understanding of this inhibitory phenomenon, we assessed whether the effector of motor responses (saccadic and manual) displays similar backward masking effects using visual stimuli. We also assessed if the visual system is the only one sensitive to the mask presentation by using an auditory task while the visual stimulus remained constant.

Conclusion

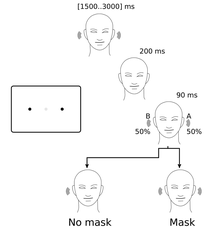
The present study offers a novel scenario involving anatomical structures upstream SC: we propose that the arrival of mask-related activity in the SC might involve structures within the basal ganglia. In particular, we questioned the role of activity in the subthalamic nucleus (STN). STN is known to suppress the motor system by inhibiting output from the basal ganglia (Alexander & Crutcher, 1990; Parent & Hazrati, 1995). The STN receives input from the frontal cortex via the hyperdirect pathway (Nambu et al., 2002), such that these executive cortical areas influence STN activity at very short latencies (Maurice et al., 1998; Magill et al., 2004). Our preliminary results in Parkinson's patients are in support of this hypothesis since the STN has been shown to lie at the heart of the system controlling response inhibition (Aron & Poldrack, 2006; Frank, 2006; Hikosaka & Isoda, 2010; Munakata et al., 2011).

Methods

Oculomotor task / Oculomanual task



Auditory-manual task



Oculomotor task After a random fixation period between 1.5 and 3 seconds, the target disappeared for 200 ms (gap period). Then, it jumped randomly leftwards or rightwards. Afterwards, two conditions were possible:

No mask The side target remained visible.

Mask After 90 ms, a structured mask grid was presented and hid the target.

Subjects were instructed to look at the central target then look at the side target.

Oculomanual task Same visual stimulus as the oculomotor task. The subjects were requested to move the mouse pointer in the direction of the target jump.

Auditory-manual task Subjects were requested to move the mouse pointer onto a central target to start a trial. A "fixation" stereo sound was played for a random duration between 1.5 and 3 seconds followed by a 200 ms "gap" during which no sound was played. Then, a mono sound was played randomly to the left or the right ear. Afterwards, two conditions were possible:

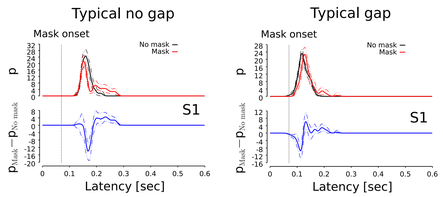
No mask The mono sound continued to be played.

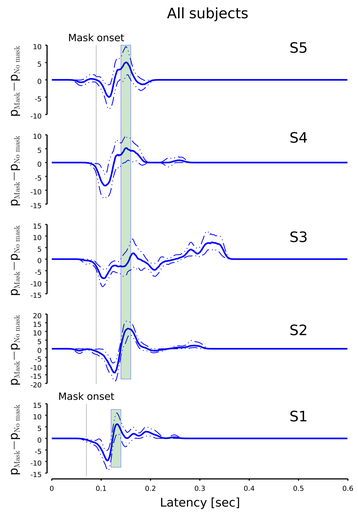
Mask After 90 ms, a stereo sound was played, masking the mono sound.

Subjects were instructed to move the arrow pointer through one of the two fixed targets presented on the screen to indicate in which ear the mono sound was played.

- Subjects were recorded using neuroClues™ by P[3]Lab for the oculomotor task.
- For the oculomanual and the auditory-manual tasks, a custom Python code was written to generate the visual and auditory stimuli.
- Latencies were extracted as the duration between the lateral target presentation and either the saccade onset (oculomotor task) or the key stroke (oculomanual/auditory-manual task).
- Latency probability distributions were computed with a bootstrap on the convolution of the latency measurements with a gaussian distribution (σ = 7.5 ms).
- Delta latency probability distributions were computed with a bootstrap on the difference of two latency distributions (as explained above).
- Percentiles 2.5, 50 and 97.5 were displayed in the different results plots.

Oculomotor task → Control subjects

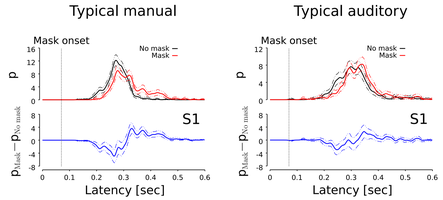


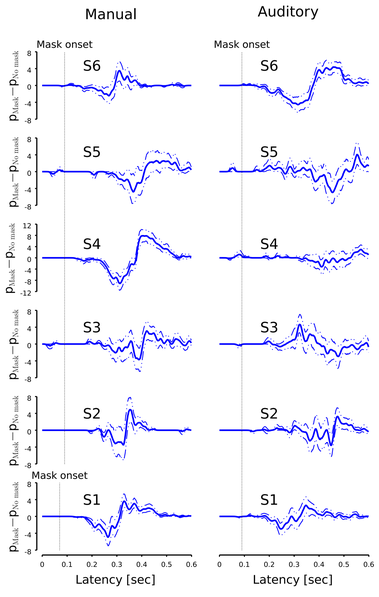


- Five subjects were recorded in the oculomotor task as controls.
- 1351 saccades were recorded out of which 1313 saccades were analyzed.
- All subjects except S1 were naive with respect to the task.
- S1 was the only subject with oculomotor knowledge (henceforth the 70 ms mask delay).
- S1 made the task with and without a gap to alter the latency distribution (Krauzlis and Miles, 1996):
  - In the no gap condition, the typical saccadic mask inhibition behavior was elicited.
  - In the gap condition, as the latencies are decreased, the mask delayed the saccades normally occuring between 0.1 and 0.12 seconds.
- All subjects had their behavior influenced by the occurrence of the mask:
  - The mask delayed saccades normally triggered during the first 20 ms of the latency distribution.

⇒ **All control subjects had their behavior modulated by the mask**

Oculomanual/Auditory-manual tasks → Control subjects

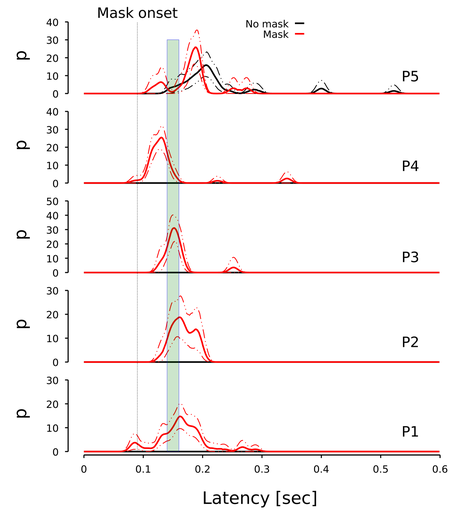




- Six subjects were recorded in the oculomanual and the auditory-manual tasks as controls.
- 3214 responses were recorded out of which 2995 responses were analyzed for the auditory-manual task.
- 3200 responses were recorded out of which 3160 responses were analyzed for the oculomanual task.
- All subjects except S1 were naive with respect to the task.
- S1 was the only subject with oculomotor knowledge (henceforth the 70 ms mask delay in the oculomanual task).
- No subject had prior knowledge about auditory tasks.
- In the oculomanual tasks, all subjects had their behavior influenced by the visual mask presentation:
  - The mask delayed saccades normally triggered during the first 40 ms of the latency distribution.
  - No subject reported any difficulties doing the oculomanual task.
  - The same delay as the one used in the oculomotor task is used.
- In the auditory-manual tasks, all subjects had their behavior influenced by the auditory mask presentation:
  - The mask delayed saccades normally triggered during the first 40 ms of the latency distribution.
  - Three subjects reported difficulties doing the oculomanual task (S2, S3 and S4). This is reflected in the smaller modulation of the base behavior.
  - The delay of the mask should be adapted for the auditory-manual task.

⇒ **Our subjects' behavior was modulated by the mask both in manual and auditory tasks. This shows that the mask induced inhibition is not acting only during oculomotor tasks. This also suggests that neural structure(s) other than SC could be involved during mask's inhibition.**

Oculomotor task → Clinical preliminary recordings



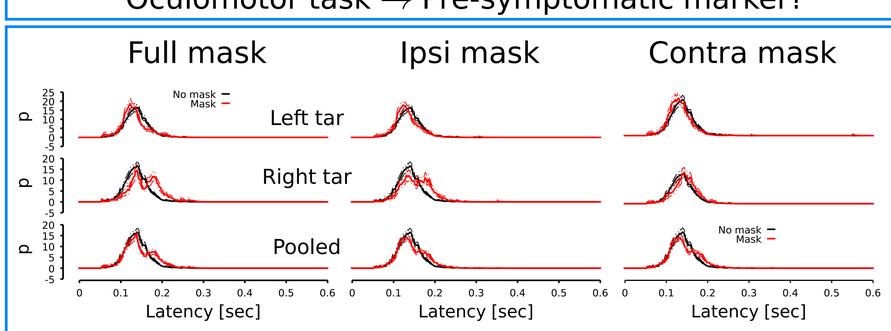
To assess if the inhibition effect observed in the control could be modulated by the Basal Ganglia, we recorded patients in the clinic.

- Five patients were recorded while doing the oculomotor task using neuroClues™:
  - Two patients came to the clinic for a suspicion of Parkinson's disease.
  - Three parkinsonian patients were recorded at bedside.
- P1-P4 latency distribution appears to be less sensitive to the mask compared to P5 and controls.
- Out of the five patients, only P5 exhibited a clear modulation of its behavior induced by the mask.
- The dip in the latency distribution of P5 is consistent with the control subjects (≈150-170 ms).

→ **P5 was the only patient with a normal DAT scan**, indicating that P5's dopaminergic neurons within the Basal Ganglia were still healthy. Henceforth, P5 was the only patient for which the Parkinson diagnosis was rejected.

These preliminary recordings point towards an involvement of the Basal Ganglia in the mask induced inhibition.

Oculomotor task → Pre-symptomatic marker?

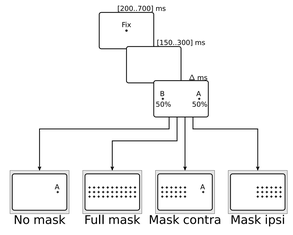


In early 2016, **24 subjects** underwent the oculomotor task. The task included a supplemental condition in which the mask either on ipsilateral to the target (thus hiding it) or contralateral to the target (leaving the target visible). Out of all the subjects recorded, **a single subject** exhibited a different behavior in response to the mask presentation. No other oculomotor behavioral response were out of the norm for this patient (e.g. antisaccade error rate, peak saccade velocity, . . .)

- Laterilized behavior:
  - Rightwards saccades were more sensitive to the mask effect.
  - Ipsilateral mask had more impact on the latency.
- Full mask behavior was mostly driven by ipsilateral mask

⇒ **This subject was diagnozed with Parkinson's disease in 2021**.

⇒ **These results point towards an early effect of the dopaminergic loss on the mask induced inhibition**.



Disclaimers. *Pierre M. Daye* is the CTO and co-founder of P[3]Lab, the company that manufactures neuroClues™. neuroClues™ is the portable laboratory solution used to record patients.
Pierre Pouget is the Scientific Advisor and co-founder of P[3]Lab, the company that manufactures neuroClues™
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