PONTIFICIA UNIVERSIDAD CATÓLICA DE CHILE
Doctorado en Neurociencias

Tesis Doctoral

Auditory processing modulation by visual working memory load

Por

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Junio 2021

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Tesis presentada a la Pontificia Universidad Católica de Chile como parte de los requisitos para optar al grado de Doctor en Neurociencias

Por

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22 Diciembre 2017

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Agradecimientos

Abstract

Top-down modulation of sensory responses to distracting stimuli by selective attention has been proposed as an important mechanism by which our brain can maintain relevant information during working memory tasks. Previous works in visual working memory (VWM) have reported modulation of neural responses to distracting sounds at different levels of the central auditory pathways. Whether these modulations occur also at the level of the auditory receptor is unknown. Here, we hypothesize that cochlear responses to irrelevant auditory stimuli can be modulated by the olivocochlear system during visual working memory. Twenty-one subjects (thirteen males, mean age 25.3 years) with normal hearing performed a visual change detection task with different VWM load conditions (high load= 4 visual objects; low load= 2 visual objects). Auditory stimuli were presented as distractors and allowed the measurement of distortion product otoacoustic emissions (DPOAE) and auditory evoked potentials (N1 and P2). In addition, the medial olivocochlear reflex strength was evaluated by adding contralateral acoustic stimulation. We found a reduction in the amplitudes of N1 responses and larger contralateral acoustic suppression of DPOAE responses during the visual working memory period. We also found a significant correlation between the individual VWM capacity and the amplitude of P2 evoked responses. These results show that the medial olivocochlear system can modulate peripheral responses to auditory distractors during a visual working memory task, and that the individual suppression of cortical responses (P2) to distracting sounds can be a predictor of visual WM performance.

INTRODUCTION

Working memory and selective attention

Working memory is the ability to maintain and manipulate information that is no longer in the environment for a short period of time (Baddeley 1983). It is fundamental for mental tasks of daily life such as language comprehension, problem solving, planning and others (Kessels and Kopelman 2012; Ma et al. 2014). One of the first important theories about working memory stays that it is decomposed in a visuospatial subsystem, a phonological loop and an episodic buffer storage commanded by a central executive system (Baddeley 1983). Moreover, a more recent theory states that working memory is not separated into subsystems, but it is a single central mechanism, shared between sensory modalities (Cowan 2005). Besides that, both theories agreed that working memory is limited in capacity, showing an average storage of 3 to 5 items (Cowan 2010). The crucial cortical structures related to working memory are the prefrontal cortex, related to the maintenance and manipulation of the information, and the posterior cortex that is involved on the storage of the information.

Another important aspect of the cognitive domain is selective attention, which is the capacity to focus on relevant sensory stimuli, while ignoring irrelevant information. Similar to working memory, selective attention has limited capacity: we cannot focus on all the incoming sensory information, and for that reason our brain use filtering mechanisms to suppress irrelevant sensory stimuli. The first theory about the mechanisms of this biological filter claimed that our nervous system can suppress non-relevant sensory responses before the semantic processing (Broadbent 1958). On the other hand, Deutsch and Deutsch (1963) proposed that there is a late

stage filter, which occurs after meaning processing. A third model was proposed by (Treisman 1964), which states that sensory information can be attenuated in early or late stages, depending on their semantic information.

In recent years, evidence suggests that attention and working memory are not separate but a single phenomenon (Cowan 2005), showing that both mechanisms are closely related, sharing similar neural networks for the top-down suppression of irrelevant stimuli (Gazzaley and Nobre 2012). These studies have demostrated that the perceptual encoding of stimuli is related to subsequent working memory performance. For example, if subjects doing a working memory task are asked to recall and respond to the last item in memory, they respond with shorter latencies and with higher accuracy, as a signature of attention (Manohar et al. 2019). In general, the ability to suppress irrelevant stimuli seems to have an important role on working memory function, as people that are able to filter out more efficiently irrelevant stimuli have shown to have higher working memory capacity (Sörqvist et al. 2012; Vogel et al. 2005).

An important theory that have attempted to explain the interaction between the attentional filter and working memory was proposed by Lavie (1995), known as the load theory. This theory predicts that an increase in working memory load reduces the limited executive resources, leading to an increase in the processing of irrelevant stimuli (Lavie et al. 2004), with several studies showing evidence for this hypothesis (Dalton et al. 2009; Lavie et al. 2004; Lavie and De Fockert 2005). However, some studies have shown the opposite, a decrease of irrelevant stimuli processing under a high working memory load (Berti and Schröger 2003; SanMiguel et al. 2008; Sörqvist et al. 2012, 2016; Spinks et al. 2004). These results have been explained by Sörqvist and Rönnberg (2014) as a protection mechanism to irrelevant information when the concentration to perform the task is increased by the increase in the working memory load.

Otoacoustic emissions and selective attention

Another important topic to the attentional filter and working memory is which nuclei from the sensory pathways are involved in the processing of the information. In relation to the auditory sensory pathway, the most peripheral stage is produced in cochlea, which is inside the inner ear. Otoacoustic emissions (OAEs) are sounds generated inside the cochlea that are transmitted outward through the middle ear and can be measured with a microphone placed in the external ear canal. There are several types of otoacoustic emissions, the most classic classification is based on the stimulus used to evoke them. In this classification there are two major types: spontaneous OAEs, that does not need an auditory stimulus to be evoke; and evoked OAEs, generated when an auditory stimulus is delivered to the ear. Evoked OAEs can be divided into three types: stimulus frequency OAE (SFOAE), distortion product OAE (DPOAE) and transient evoked AOE (TEOAE). DPOAEs are created when two simultaneous pure tones are delivered to the cochlea, creating vibrations in places of the basilar membrane different from the vibrations of the two tones, an effect caused by the nonlinear characteristics of the cochlear amplifier (Robles et al. 1991, 1997).

OAEs are produced as a byproduct of the cochlear amplification mechanism of the outer hair cells (OHC). This mechanism is active and responsible for the nonlinear characteristics of cochlear responses, and to the high sensitivity and frequency selectivity of the inner ear (Robles and Ruggero 2001). The cochlear amplification mechanism works by providing additional energy that increases the vibration of the basilar membrane just at the peak of the traveling wave, allowing the amplification of low energy stimuli (Davis 1983). It is produced mainly by the action of OHC. These cells are organized in three rows along the cochlea and have the ability to

change their size via an electromotility mechanims which depends on prestin, a membrane protein of OHC (Zheng et al. 2000).

OHC are the main synaptic target of the medial olivocochlear (MOC) bundle, the final stage of the auditory efferent system. The auditory efferent system comprises descending projections from pyramidal neurons of layers V and VI of the auditory cortex to several subcortical nuclei of the ascending auditory pathway, including the medial geniculate body, inferior colliculus, cochlear nucleus, and the superior olivary complex, forming a neural network of multiple feedback loops that reaches the cochlear receptor through olivocochlear neurons (Perrot et al. 2006; Saldaña 2015; Terreros and Delano 2015; Yakunina et al. 2019). Given the large efferent innervation of OHCs by the medial olivocochlear bundle, these efferent pathways are proposed to function as a biological filter that can modulate cochlear and auditory nerve responses during selective attention tasks (Terreros et al. 2016). Importantly, it has been shown that the activation of the MOC produces an inhibition of the cochlear amplifier gain, decreasing the amplitude of OAEs (Guinan 1990; Siegel and Kim 1982; Veuillet et al. 1991). In addition to cortical connection, the MOC can be activated by contralateral acoustic stimulation (CAS) of the contralateral ear, known as the contralateral MOC-reflex. The contralateral MOC-reflex is a neural circuit that connects the cochlea from one ear to the other: from the cochlear nucleus of the contralateral ear, the signal cross the middle section of the brainstem to the ipsilateral MOC nucleus, and from there goes to the ipsilateral cochlea by the MOC.

Many studies have shown evidence for a cortifugal modulation of cochlear and auditory nerve responses. In animals, for example, a reduction of auditory-nerve responses during visual attention was obtained in cats and chinchillas (Oatman 1971; Delano et al., 2007), while electrical stimulation of cortical neurons have shown to modulated cochlear microphonics

(which are dependent on OHCs activity) in bats (Xiao and Suga 2002) and chinchillas (Dragicevic et al. 2015). Human studies have focused on changes in otoacoustic emissions by visual and auditory selective attention tasks. The first study of this kind was made by Puel et al. in 1988, using click evoked otoacoustic emissions (CEOAEs), a type of TEOAE, showing a reduction in amplitude when the subject was doing a visual selective attention task. This study was followed by others showing similar results (Avan and Bonfils 1992; Froehlich et al. 1990), but finally criticized for the role of arousal in their results (Michie et al. 1996). Other studies have assessed the combined role of CAS and visual selective attention on OAEs (de Boer and Thornton 2007; Ferber-Viart et al. 1995), or investigated the interaural auditory attention effect on the OAEs by using a dichotic listening task (Srinivasan et al. 2014; Stephane Maison et al. 2001). More recent studies using DPOAEs have focused on comparing the changes in DOAEs between auditory and visual selective attention tasks (Dragicevic et al. 2019; Smith et al. 2012; Srinivasan et al. 2012; Wittekindt et al. 2014), showing no conclusive results. All selective attention studies reviewed above have in common the use of perceptual tasks to evaluate the role of cortifugal modulation, with no working memory load manipulation on their tasks.

Like OAEs, the auditory brainstem response (ABR) (the auditory evoked potentials that appear between 1 and 10 ms after stimulus onset), have been studied on their role on selective attention tasks but with no conclusive results of whether they can be modulated by selective attention (Hirschhorn and Michie 1990; Lukas 1981).

As discussed above, in recent years working memory have been taken into account as an important factor to the attentional filter, and recent studies have shown that brain responses to distracting sounds are modulated at the cortical level during visual working memory (Simon et al. 2016; Sörqvist et al. 2016; Tusch et al. 2016) and also at the subcortical level (Sörqvist et al.

2012). For instance, Sörqvist and colleagues (2012) showed that the amplitude of the wave V of ABR to irrelevant sounds is reduced during a visual-verbal working memory task. Additionally, they found that the difference of the ABR response between low and high visual-verbal working memory load was increased in high working memory capacity individuals. These findings show that ascending auditory midbrain responses can be modulated by visual-verbal working memory and that the working memory capacity could be related to the degree of modulation, but whether WM also modulates more peripheral auditory structures, like the cochlear receptor is still unknown.

Here, we hypothesized that, similar to visual selective attention paradigms, cochlear responses can be modulated during a visual working memory task. To address this proposal, we modified a classic paradigm of visual working memory (Luck and Vogel 1997) by incorporating distracting acoustic stimuli at different periods of the task to measure cochlear and cortical auditory responses during different working memory states. A pair of tones (f1 and f2) that elicit DPOAE were delivered to one ear, while a broadband noise was presented to the contralateral ear. These bilateral acoustic distractors were presented during the visual WM task, and allowed the evaluation of the medial olivocochlear reflex strength. Additionally, simultaneously to DPOAEs, auditory evoked potentials N1-P2 were measured as a signature of early cortical auditory responses using electroencephalographic (EEG) recordings, allowing us to investigate sensory receptor and cortical responses of auditory distractor stimuli evoked in a visual working memory task.

HYPHOTESIS

Otoacoustic emissions and early auditory evoked potentials (N1 and P2) are attenuated during increased visual working memory load conditions.

Specifically, we predict that:

1) Otoacoustic emissions suppression by CAS will be reduced as the visual working memory load is increased.
2) Auditory N1 and P2 will be reduced as the visual working memory load is increased.
3) Subjects with high visual working memory capacity will have higher reductions in otoacoustic emissions and auditory N1 and P2 as visual working memory load increased.

OBJECTIVE

Understand the relationship between visual working memory and cortical and subcortical responses to auditory distracting stimuli.

Specific objectives

1) Analyze if otoacoustic emissions are modulated by visual working memory load.
2) Analyze if the auditory N1 and P2 is modulated by visual working memory load.
3) Understand how the variation in visual working memory capacity is related with the processing of distracting auditory stimuli.

MATERIALS AND METHODS

Subjects. Twenty-one participants (13 males, mean age ± standard deviation: 25.3 ± 3.1 years, range 20 – 31 years) were recruited. All subjects were evaluated with air-conduction pure-tone audiometry to ensure normal hearing thresholds (≤ 20 dB HL) at different frequencies (125–8000 Hz) using a clinical audiometer (AC40, Interacoustics®). All participants had normal to normal-corrected vision. The study was approved by the Ethics Committee of the Clinical Hospital of the University of Chile. All subjects gave written informed consent.

Experimental procedures

Behavioral paradigm. The visual working memory task was based on a visual change detection paradigm described by Luck and Vogel (1997) that was modified by adding DPOAE eliciting tones (primary tones f1 and f2, ipsilateral) and CAS as irrelevant acoustic stimuli (Figure 1). All stimuli presentations (visual and auditory), behavioral responses, data acquisition and synchronization (EEG and DPOAE) were controlled by a custom software written in C Language (LabWindows™/CVI 9.0, National Instruments®) using a multifunction board (PCIe-6321, National Instruments, Texas, US) housed in a desktop computer.

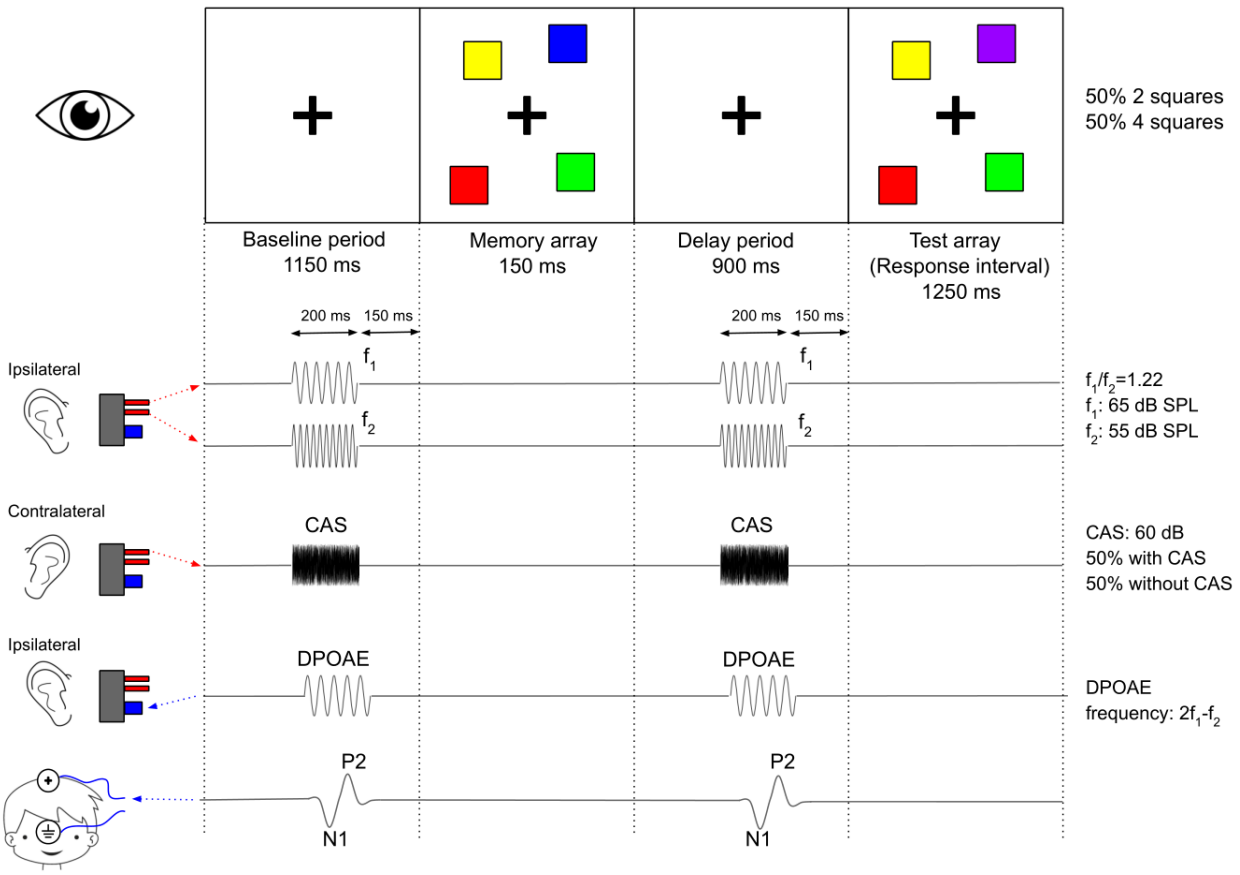

Figure 1. **Diagram of the visual working memory task with distracting sounds.** The trial begins with a baseline period. Subjects must maintain ocular fixation in the cross during all the task. 350 ms before the memory array period begins, an auditory distractor of 200 ms is presented in the "baseline period". In half of the trials this auditory distractor corresponds only to the DPOAE eliciting tones (f1 and f2, ipsilateral channel), while in the other half of the trials the distracting sound is constituted by the ipsilateral DPOAE eliciting tones and the CAS. In the memory array period, an array of four- or two-colored squares appear for 150 ms in the visual display. Subjects are instructed to keep the squares in mind during a delay period of 900 ms and respond in the test array period. A second set of the same distracting auditory stimuli is presented 350 ms before the beginning of the test array period. Then, a second set of four- or two-colored squares appears for 1250 ms, and subjects have to answer whether one square has changed its

color or not (in the figure, blue change for purple square). Two conditions were used: low (2 colored squares) and high WM load (4 colored squares, shown in the figure). DPOAE and N1-P2 auditory evoked potentials were recorded in response to auditory stimuli in the baseline and delay periods. Red arrows show signals that were delivered to the ear, while blue arrows illustrate signals that were acquired for analysis. CAS: contralateral acoustic stimulation (broadband noise); DPOAE: distortion product otoacoustic emission.

Visual stimuli. We used two or four colored squares (0.65° x 0.65°) that appeared randomly in a rectangular region of 9.8° x 7.3° at the center of a computer screen, with a grey background. Colors were chosen randomly from a set of 9 colors (red, blue, yellow, green, white, purple, black, pink, orange) with no repeated colors in each array. A black fixation cross at the center of the screen was maintained during the task. Distance between the centers of the squares was at least 2° and between the center of the squares and fixation cross was at least 3°. Distance between the participants and the screen was 70 cm. Two working memory load conditions were used: low (2 squares each array) and high working memory load (4 squares each array). Subjects were instructed to look at the fixation cross during the task. VWM capacity was computed using the formula $K = S(H-F)/(1-F)$, were K is the VWM capacity index, S is the number of squares, H is the hit rate and F is the false alarm rate (Cowan 2001; Pashler 1988; Rouder et al. 2011). Only high WM load condition was used (4 colored squares) to compute K.

Auditory stimuli. We used two tones (f1 and f2 or primary tones) that elicit DPOAE with and without contralateral acoustic stimulation (broadband noise) as auditory distractors during the visual WM task. Primary pure tones f1 and f2 lasted for 200 ms (rise/fall time of 10 ms) and had

sound pressure levels of 65 dB for f1 and 55 dB for f2. Because of the non-linearity of the cochlea, when the two primary tones (f1 and f2) are simultaneously presented, DPOAEs are generated at frequencies that are linear combinations of the primary frequencies (Robles et al. 1991; Robles et al., 1997). In the present work, the 2f1-f2 combination was chosen as these DPOAEs displayed the largest amplitudes compared to other combinations. In addition, the frequency of the f2 tone was chosen individually in the range of frequencies between 1.25 and 2.2 kHz, using a f2/f1 ratio of 1.22. This method allowed us to obtain the largest 2f1-f2 DPOAEs amplitudes in each subject between 1.0 and 1.45 kHz. Primary tones were presented in the ipsilateral ear in all trials, while in half of the trials, a 60 dB SPL broadband noise was presented in the contralateral ear, simultaneously with the two primary tones (even trials). The purpose of adding the contralateral noise or CAS is to elicit the MOC-reflex, activating the ipsilateral efferent system that have been shown to reduce the cochlear gain (Robles & Ruggero 2001), and consequently, the effect of visual working memory will be tested on the DPOAE MOC-reflex strength (or CAS effect on DPOAE).

Auditory stimuli (DPOAE and CAS) were generated with a multiprocessor device at 48.8 kHz (RZ6, Tucker-Davis Technologies®, US), controlled with a National Instrument board (PCIe-6321), and delivered using two transducers (ER-10C, Etymotic Research®, US) inserted in the left and right ear canals. DPOAEs were recorded using ER-10C system microphone (40 dB amplification) and digitized using RZ6 hardware at a sampling rate of 48.8 kHz. The laterality of the chosen ear (left or right) for delivering the DPOAE eliciting tones (ipsilateral) was balanced across subjects.

Temporal course of the behavioral paradigm. Trials started with a baseline period of 1150 ms, in which only the fixation cross is presented. During baseline, a first set of auditory stimuli (ipsilateral channel: f1 and f2; and contralateral channel: CAS in half of the trials) are presented 350 ms before the end of this period. After the baseline period, an array of colored squares appears briefly for 150 ms (memory array). Subjects are instructed to keep in mind these colors for 900 ms (delay period). During the delay period, a second set of auditory stimuli (DPOAE and CAS) are presented 350 ms before the onset of the second array of colored squares (test array). The positions of the colored squares were the same for memory and test array in each trial, and in half of the trials, only one square changed its color randomly. During the test array, subjects had to respond, in a 1250 ms response window, whether a single square had changed its color or not. At the end of trials, a temporal jitter (± 50 ms) was added.

A total of 30 trials were included in one block of two- or four-colored squares (low and high WM load respectively). Participants made one block of each WM load condition before starting the protocol. The volunteers made 20 blocks in total, with a 20 seconds rest time period between blocks, and one pause of 15 minutes after finishing ten blocks. Calibration of the auditory stimuli was performed before the task and between blocks to confirm sound pressure levels. EEG and DPOAE responses to auditory stimuli were recorded during the baseline and delay periods with low or high visual WM load conditions (four different situations). In addition, DPOAE eliciting tones were presented with or without contralateral noise in a balanced manner (50% of the trials had CAS), totalizing eight different conditions. DPOAEs and N1-P2 evoked potentials were recorded in each of the eight conditions with 150 trials per condition.

Data analyses

2f1-f2 DPOAE amplitudes were obtained by averaging the cochlear responses recorded on each condition and applying a fast Fourier transform (flat top window, 5 Hz bandwidth). Then, the amplitude of the 2f1-f2 frequency component was computed for each subject (see Figure 2 for a DPOAE signal example). DPOAE amplitudes with at least 6 dB signal-to-noise ratio were further analyzed, with an average rejection rate across subjects of 9.2%. After the signal-to-noise ratio criterion for DPOAE rejection, we used the median absolute deviation (Leys et al. 2013) to take into account larger changes in the sound pressure due, for example to swallowing or foam movements in the external ear canal. The combined average rejection rate across subjects with both methods for DPOAE was 14.5%.

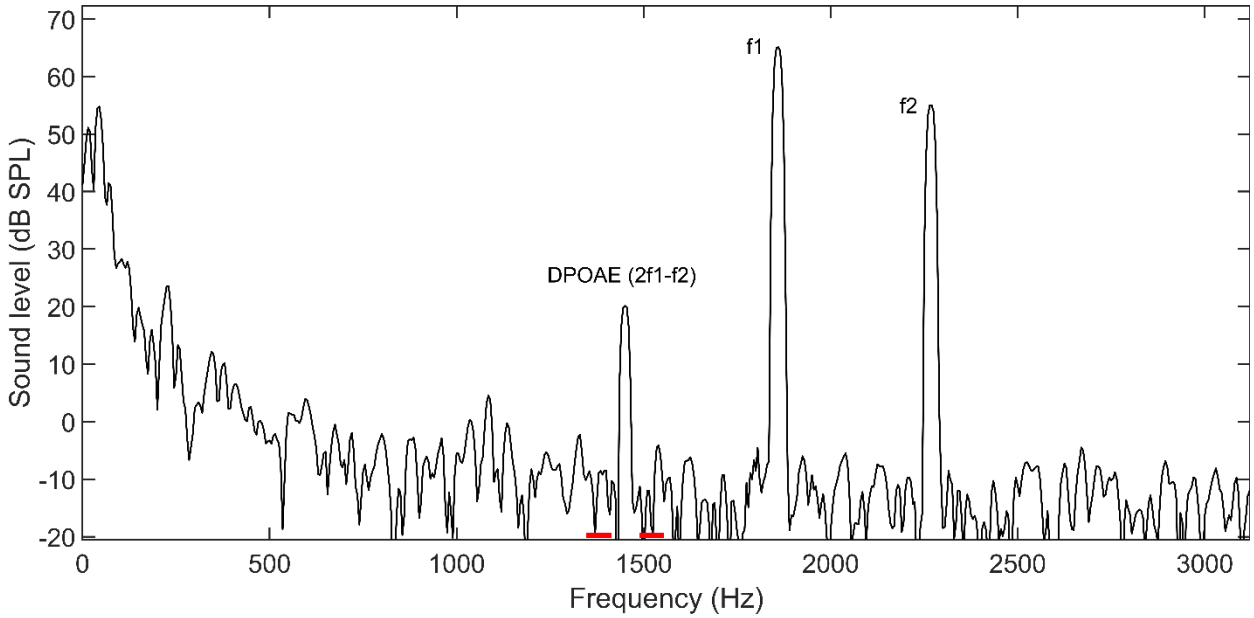

Figure 2. Spectrum of the microphone signal for DPOAE-eliciting tones. The plot shows an example of a 2f1-f2 DPOAE recorded in one subject during the experiment. Depicted are the primary tones f1 and f2, and the DPOAE in the frequency 2f1-f2. In red are the frequencies used

to obtain the noise floor in this DPOAE (20 Hz from each side of the peak, not scaled in the figure).

CAS effect on DPOAEs amplitude during the visual WM task.

CAS effect on DPOAE amplitude was calculated by measuring the amplitude difference of DPOAEs recorded with and without contralateral noise. After that, CAS effect on DPOAE (measured in dB) was also compared between baseline and delay periods and between each visual WM load condition (low and high WM).

Noise floor level analysis

The noise floor level of DPOAEs were compared between conditions as previous works found that the noise level can be modulated during selective attention tasks (Francis et al. 2018). The noise floor level was computed as the mean amplitude of the signal in the 2f1-f2 DPOAE frequency vicinity (20 Hz were computed from each side, in red in figure 2, not scaled). Then, the noise floor for each DPOAE that have passed the rejection criteria was averaged in each condition for each subject. The same statistic procedure used for DPOAE was applied for the noise floor analysis.

Electroencephalographic recordings and analyses

EEG was recorded using 29 passive electrodes (Fp1, Fp2, F3, Fz, F4, Ft9, Fc5, Fc1, Fc2, Fc6, Ft10, T7, C3, Cz, C4, T8, Tp9, Cp5, Cp1, Cp2, Cp6, Tp10, P7, P3, Pz, P4, P8, O1, O2) mounted in an elastic cap (EasyCap®, Brain Products, Germany) and placed on the scalp according the international 10-20 electrode placement system. Eye blinks were monitored using

an electrode placed at the inferior right eye. EEG was recorded using AFz as a ground and the reference electrode was placed at the tip of the nose. Impedance was maintained below 5 kΩ in all subjects during the experiment. Data was digitized at a sampling rate of 500 Hz. EEG recordings were made using a low-impedance amplifier (PZ6 amplifier, Tucker-Davis Technologies®) (frequency response: 3 dB, 0.1 Hz - 5 kHz) connected to a I/O multiprocessor device (RZ6, Tucker-Davis Technologies®).

EEG data processing was made using EEGLAB software (Delorme and Makeig 2004). Data were down sampled to 250 Hz and filtered from 0.5 to 20 Hz. We used EEGLAB to reject larger artifacts (mean rejection rate = 4.75%), while independent component analysis was used to remove (Makeig et al. 1997) eye blinks components and artifacts. Epochs of 1350 ms were extracted at the beginning of the onset of each auditory stimulus and then, using a baseline of 200 ms included in the epoch, the mean value of the baseline was extracted from each point of the epoch. Data were averaged on each of the eight conditions, using only trials with correct responses. The amplitudes of N1-P2 auditory evoked potentials were computed as the mean amplitude of the peak (20 ms each side) in the Cz electrode. The peak amplitude of N1 was the largest negative peak between 50 ms and 150 ms, while P2 peak amplitude was the first positive peak after N1. Latency of N1-P2 was computed as the latency of the peak amplitude.

Addittional control test

Additionally, we performed a control experiment with 10 new subjects (6 males, mean age ± standard deviation: 30.3 ± 5.7 years, range 23-42 years). The experimental procedure and data analysis were the same as described above but subjects were required to look at the fixation cross in the screen and do not perform the task. All subjects were evaluated with air-conduction pure-

tone audiometry to ensure normal hearing thresholds (≤ 20 dB HL) at different frequencies (125–8000 Hz) using a clinical audiometer (AC40, Interacoustics®). In eight subjects we evaluated the thresholds for middle-ear muscles (MEM) reflex activation using offline measurements of the external ear canal acoustic immittance with a clinical device (AT235H, Interacoustics, Denmark). MEM reflex thresholds were always obtained with tones and broad band noise stimuli above 75 dB HL All subjects had normal to normal-corrected vision. The same electroencephalographic equipment and protocol described above was used for the control experiment.

Statistics. Normal distribution of data was evaluated using Shapiro-Wilk tests. For EEG data we compared the eight different conditions using a three-way repeated measures (RM) ANOVA with two levels each factor (factors: (1) task period: baseline or delay period, (2) visual WM load: low or high, (3) CAS: with or without CAS). For DPOAE data the CAS effect on DPOAE was obtained in the baseline and delay period, and in the low and high visual working memory load conditions. Two-way repeated measures ANOVA was used in the DPOAE suppression by CAS data to compare between (1) task period (baseline or delay period) and (2) visual WM load (low or high WM load). For analysis purposes, the “delay period” was considered as the “visual working memory period”, therefore in this work, these names are considered as synonyms. Statistical correlations were computed with Pearson's tests, using DPOAE amplitudes, VWM individual capacities and N1-P2 evoked potential amplitudes.

RESULTS

Behavioral data

The mean hit rate for the 4-square visual WM condition was 82 % (SD 11) while the performance for the 2-square condition was significantly better (figure 3A, mean hit rate = 93 % (SD 5); paired t-test, $t_{(20)}$ = -5.43, p < .001). The mean reaction times for the high and low WM load conditions were also significantly different, with 694 ms (SD 100) for the 4-square condition, and 657 ms (SD 117) for the 2-square (figure 3B, paired t-test, $t_{(20)}$ = 5.56, p < .001). The mean VWM capacity (K) The mean VWM capacity (K) was 3.21 (SD 0.54) squares, with a range between 1.79 and 3.95.

A **B**

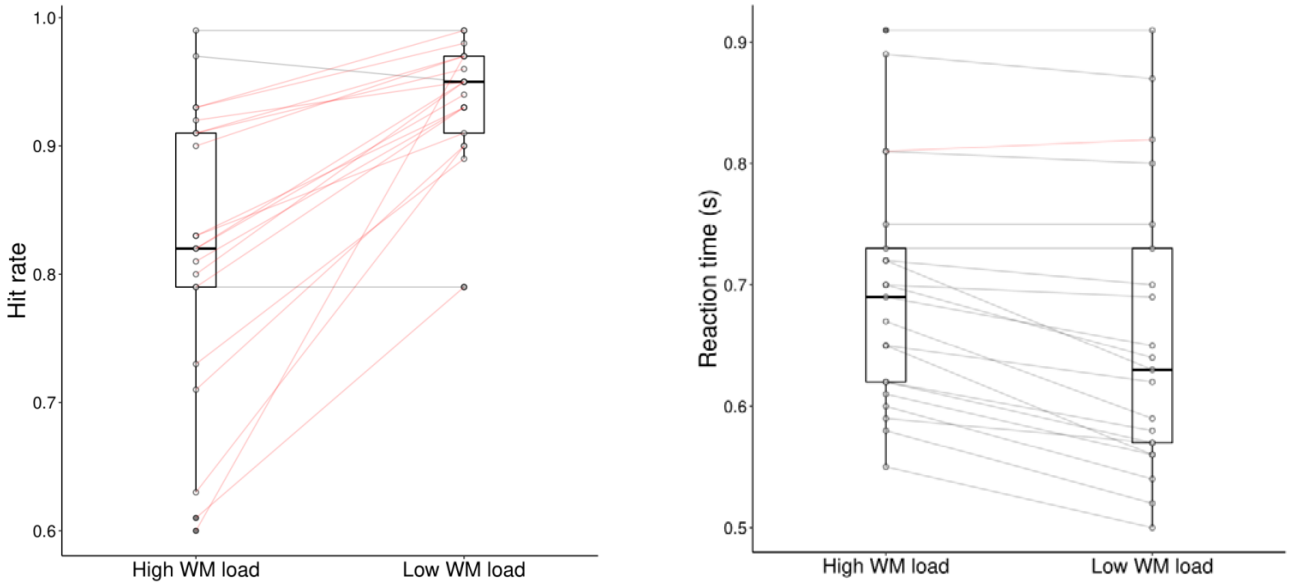

Figure 3. Boxplot of hit rate and reaction time responses. The hit rate **(A)** was reduced during the high WM load condition (paired t-test, $t_{(20)}$ = -5.43, p < 0.001), while the reaction time (**B)** was reduced during low WM load (paired t-test, $t_{(20)}$ = 5.56, p < .001).

Red lines show hit rate and reaction time responses increments in the low WM load condition.

Non-significant differences were found when comparing the mean hit rate and reaction times between trials with and without contralateral noise for each WM load condition (Table 1).

Condition	**Hit rate**	**Statistics (CAS vs no CAS)**	**Reaction time**	**Statistics (CAS vs no CAS)**
Low WM load with CAS	93 % (SD 6)	Paired t-test, $t_{(20)}$ = 0.12, p =0.90	661 ms (SD 121)	Paired t-test, $t_{(20)}$ = 1.68, p =0.11
Low WM load without CAS	93 % (SD 6)		653 ms (SD 114)	
High WM load with CAS	82 % (SD 13)	Paired t-test, $t_{(20)}$ = -0.22, p =0.82	697 ms (SD 98)	Paired t-test, $t_{(20)}$ = 0.83, p =0.42
High WM load without CAS	82 % (SD 11)		692 ms (SD 99)	

Table 1. Behavioral performance in low and high working memory load conditions. There are no differences in hit rate and reaction times between CAS and no CAS trials.

EEG results

All statistical EEG analysis were made using repeated measures three-way ANOVA and Bonferroni posthoc test. Figure 4 shows the grand average of auditory evoked potentials (N1 and P2) recorded at electrode Cz during the baseline and visual working memory periods. N1 and P2 amplitudes were significantly reduced during the visual working memory period (delay period) when compared to the baseline period (Figure 4A, N1 mean amplitude: baseline period: -3.62 μV (SD 1.52); delay period: -2.46 μV (SD 1.36); main effect of task period: $F[1,20] = 34.61$, $p < 0.001$, $n_p^2 = 0.63$; Figure 4B, P2 mean amplitude: baseline period: 2.96 μV (SD 1.36) ; delay period: 1.59 μV (SD 1.29); main effect of task period: $F[1,20] = 30.74$, $p < 0.001$, $n_p^2 = 0.61$). In figure 5 are the boxplots from figure 4 data, showing that 19 subjects had a reduction in the N1 amplitude (figure 5A) from baseline to visual WM period while 20 subjects in the P2 amplitude (figure 5B) had the same reduction.

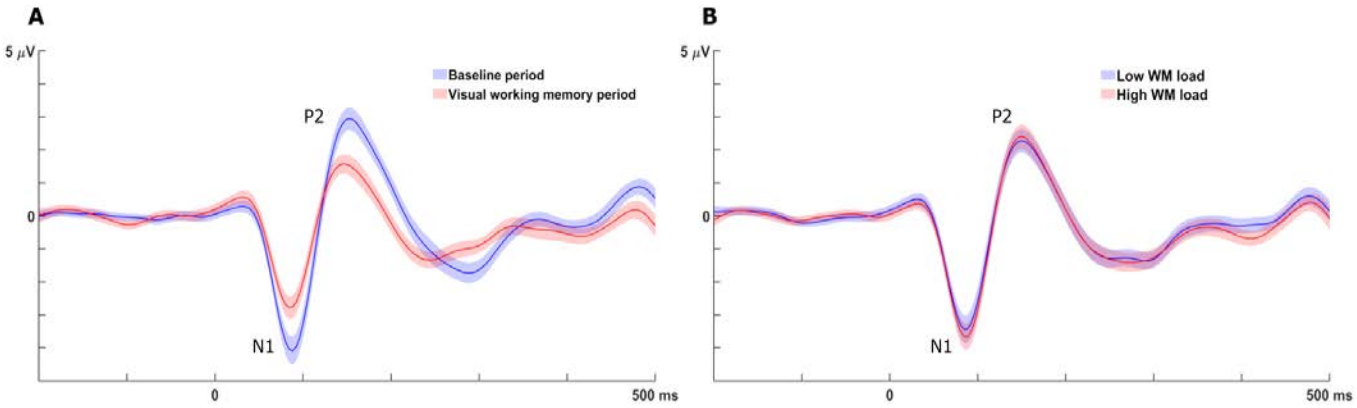

Figure 4. Grand average (N = 21) of auditory evoked potentials (N1 and P2) to distracting auditory stimuli recorded at electrode Cz in the electroencephalogram in (A) the baseline (blue line), visual working memory (red line) period, and in (B) the low (blue) and high (red) WM load conditions. Standard error is depicted for each trace as a shaded color.

Zero time is coincident with the onset of the auditory stimuli. N1 appears as the first negative component with a peak around 90 ms and P2 as the next positive component with a peak around 150 ms. Significant amplitude differences were obtained when comparing (A) the baseline with the VWM evoked potentials (N1: main effect of task period: F[1,20] = 34.61, p < 0.001, n_p^2 = 0.63; P2: main effect of task period: F[1,20] = 30.74, p < 0.001, n_p^2 = 0.61), while (B) non-significant amplitude differences were found when comparing the average N1 and P2 responses obtained in the high and low visual working memory load conditions (N1: main effect of WM load: F[1,20] = 0.68, p = 0.41, n_p^2 = 0.03; P2: main effect of WM load: F[1,20] = 0.21, p = 0.64, n_p^2 = 0.01). Statiscal analysis were made using repeated measures three-way ANOVA and Bonferroni posthoc test.

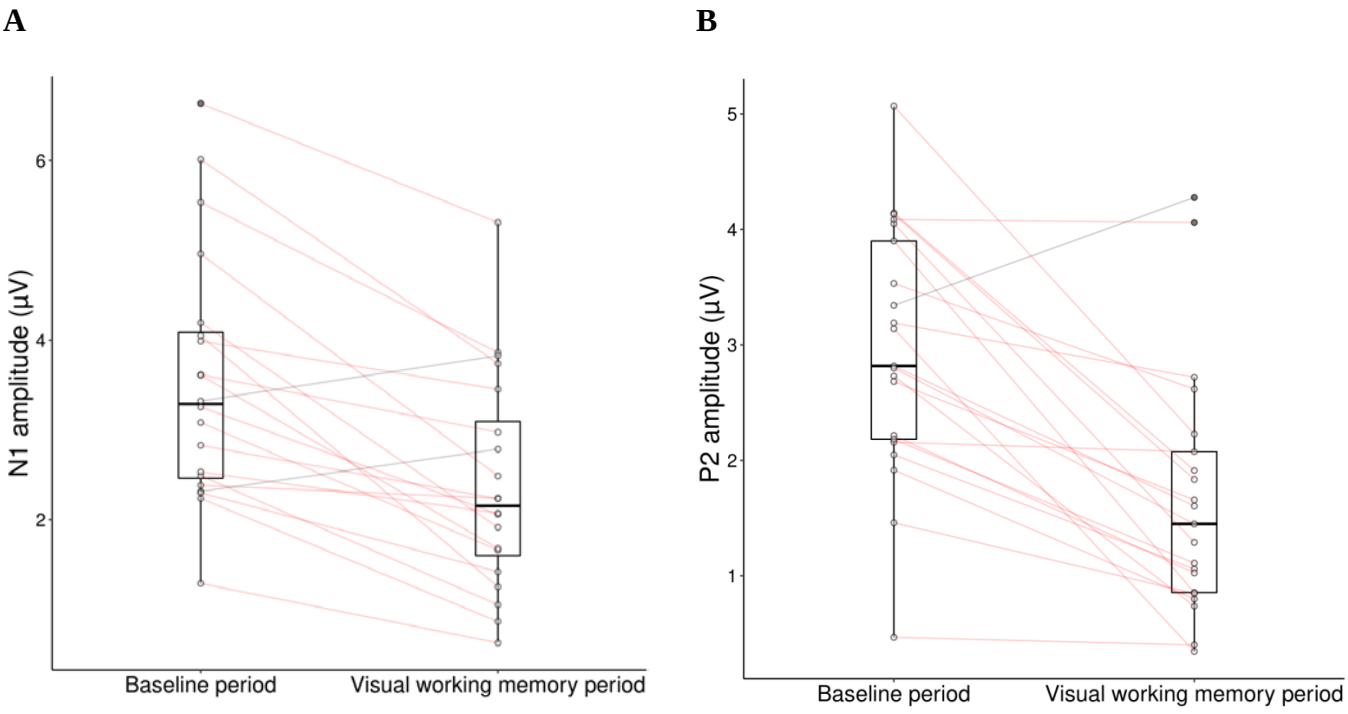

Figure 5. Auditory cortical N1 and P2 amplitudes during the baseline and visual working memory period. Boxplots data are depicted from figure 4A data, showing individual

N1 (absolute values) **(A)** and P2 **(B)** changes in amplitude from baseline to visual WM period. For each subject, red lines show individual reductions in amplitudes in the visual working memory period (N1: 19 subjects; P2: 20 subjects).

No amplitude effect was found in auditory evoked potentials when comparing the low and high visual WM load conditions (N1 mean amplitude: low WM: -2.99 μV (SD 1.60); high WM: -3.09 μV (SD = 1.52) ; main effect of WM load: F[1,20] = 0.68, p = 0.41, n_p^2 = 0.03; P2 mean amplitude: low WM: 2.25 μV (SD = 1.46); high WM: 2.29 μV (SD = 1.52); main effect of WM load: F[1,20] = 0.21, p = 0.64, n_p^2 = 0.01).

No significant effect of contralateral noise was found on N1 amplitude (Figure 6A, N1 mean amplitude: without CAS: -2.93 μV (SD = 1.28); with CAS: -3.15 μV (SD = 1.32); main effect of CAS: F[1,20] = 2.45, p = 0.13, n_p^2 = 0.11). Meanwhile, a significant effect of contralateral noise was found in P2 amplitude (figure 6B, P2 mean amplitude: without CAS: 1.89 μV (SD = 0.83); with CAS = 2.65 μV (SD = 1.21); main effect of CAS: F[1,20] = 30.77, p < 0.001, n_p^2 = 0.51). Additionally, there was a statistical significant interaction effect of CAS and task period in P2 amplitude (Figure 7, F[1,20] = 14.23, p = 0.001, n_p^2 = 0.42). Post hoc analysis shows a statistical significant difference between P2 amplitude with and without CAS in the baseline period (p < 0.001), but no significant difference in the visual working memory period (p = 0.23). No significant effects were found in N1 amplitude on the interaction effect of task period and CAS (F(1,20) = 1.30, p = 0.26, n_p^2 = 0.06).

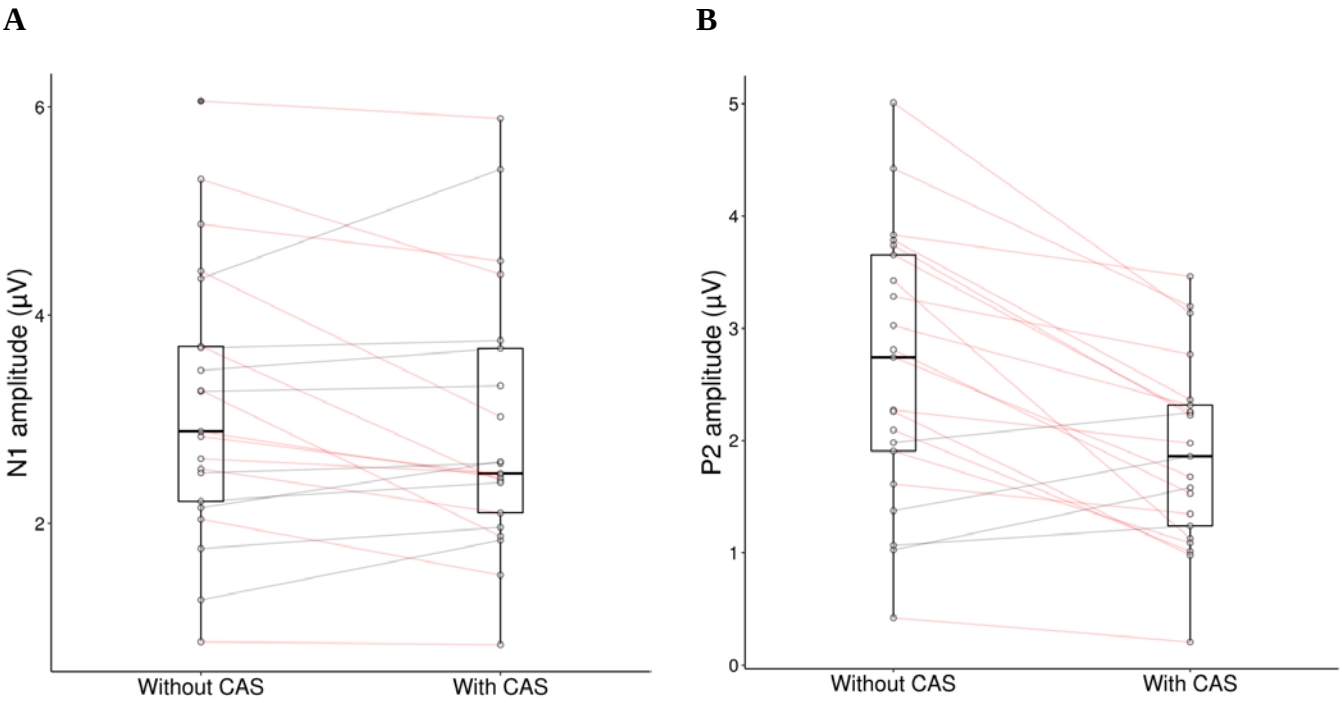

Figure 6. Auditory cortical N1 and P2 amplitudes with and without contralateral noise. A. No significant difference was found between N1 amplitude with and without CAS (repeated measures three-way ANOVA, main effect of CAS: F[1,20] = 2.45, p = 0.13, n_p^2 = 0.11). Red lines shows that 9 subjects had a reduction in N1 amplitude without contralateral noise. **B.** A significant difference was found between P2 amplitude with and without CAS (repeated measures three-way ANOVA, main effect of CAS: F[1,20] = 30.77, p < 0.001, n_p^2 = 0.51). Red lines shows that 17 subjects had a reduction in P2 amplitude without CAS.

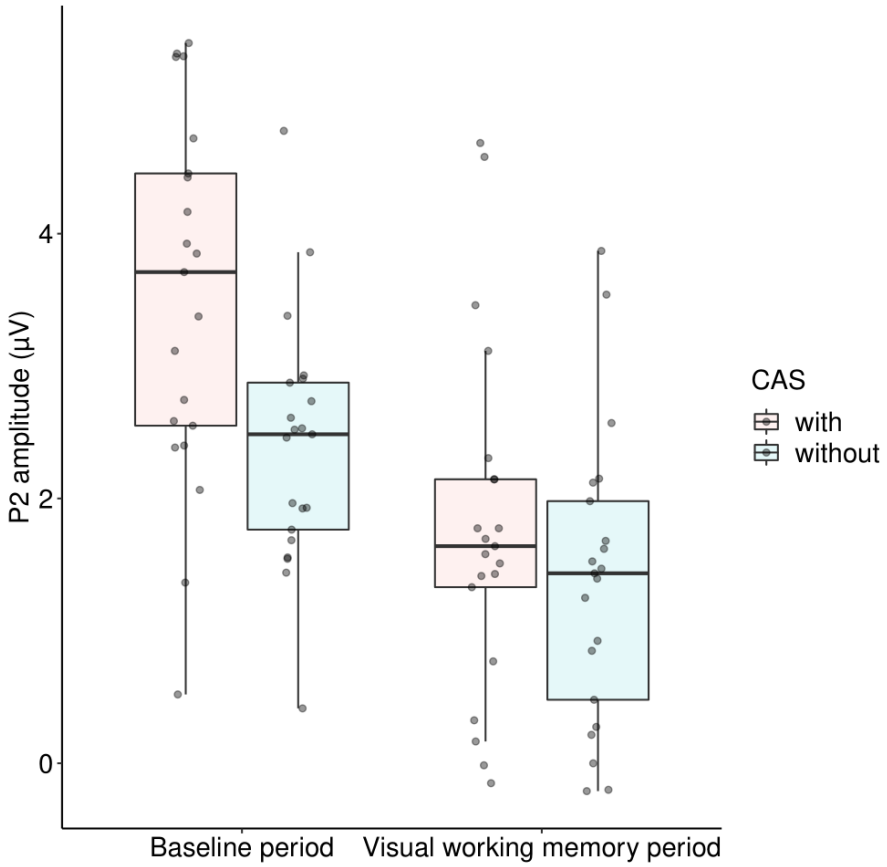

Figure 7. Auditory cortical P2 amplitudes with and without contralateral noise in the baseline and visual working memory period. There was a statistical significant interaction effect of task period and CAS (RM three-way ANOVA, F[1,20] = 14.23, p = 0.001, n_p^2 = 0.42). Post hoc analysis showed a significant reduction between P2 amplitude with and without CAS in the baseline period ($p < 0.001$), but no significant difference in the visual working memory period ($p = 0.23$).

The mean latency of N1 evoked potentials (Figure 8A) in the baseline period was 87.8 ms (SD = 8.2), while in the delay period was 85.9 ms (SD = 8.3), with no significant difference between them (main effect of task period: F(1,20) = 2.57, p = 0.12, n_p^2 = 0.11). The mean latency of P2 (figure 8B) in the baseline period was 152.5 ms (SD = 14.5), while in the delay period was

147.4 ms (SD = 15.2), with a significant difference between them (main effect of task period: F(1,20) = 14.43, p = 0.001, n_p^2 = 0.42).

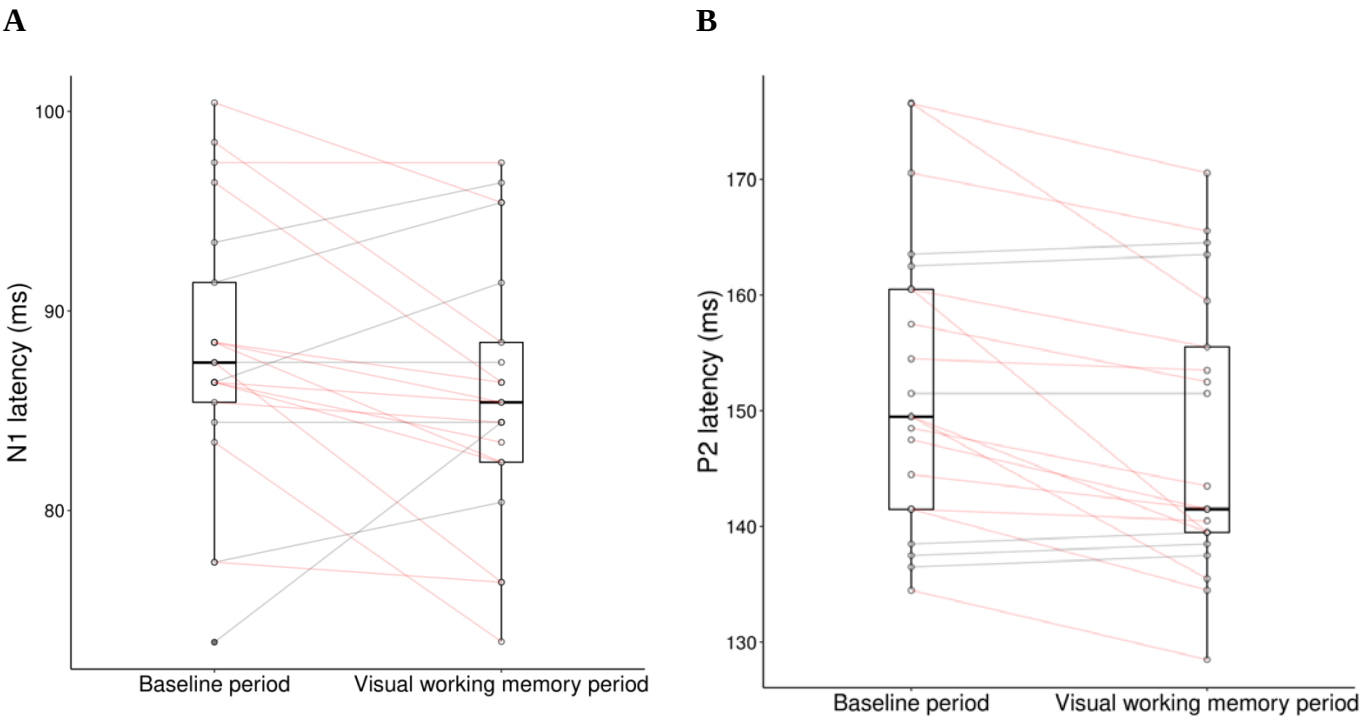

Figure 8. Auditory cortical N1 and P2 latencies during the baseline and visual working memory period. A. No difference was found in N1 latencies between the baseline and visual WM period (RM three-way ANOVA, main effect of task period: F(1,20) = 2.57, p = 0.12, n_p^2 = 0.11). Red lines show that 13 of a total of 21 subjects had a reduction in latencies in the visual working memory period **B.** A significant difference was found between the baseline and visual WM period in P2 latencies (RM three-way ANOVA, main effect of task period: F(1,20) = 14.43, p = 0.001, n_p^2 = 0.42). Red lines show that 14 of a total of 21 subjects had a reduction in latencies in the visual working memory period.

Comparison between N1 and P2 latencies in low and high WM load did not show any significant effect (N1 mean latency: low WM load: 86.6 ms (SD = 6.09); high WM load: 87.1 ms

(SD = 5.87); main effect of WM load: F(1,20) = 0.30, p = 0.58, n_p^2 = 0.01; P2 mean latency: low WM load: 150 ms (SD = 12.1); high WM load: 150 ms (SD = 12.6); main effect of WM load: F(1,20) = 0.03, p = 0.861, n_p^2 = 0).

Finally, N1 and P2 latencies without and with CAS were compared. N1 latencies showed a significant reduction with CAS (Digure 9A, N1 mean latency: without CAS: 88.8 ms (SD = 6.73); with CAS = 85 ms (SD = 6.09); main effect of CAS: F(1,20) = 22.10, p < 0.001, n_p^2 = 0.52). P2 latencies showed a significant reduction with CAS (figure 9B, P2 mean latency: without CAS: 153 ms (SD = 12.6); with CAS = 147 ms (SD = 12.3); main effect of CAS F(1,20) = 22.10, p = 0.003, n_p^2 = 0.37). Table 2 shows resume of the EEG results.

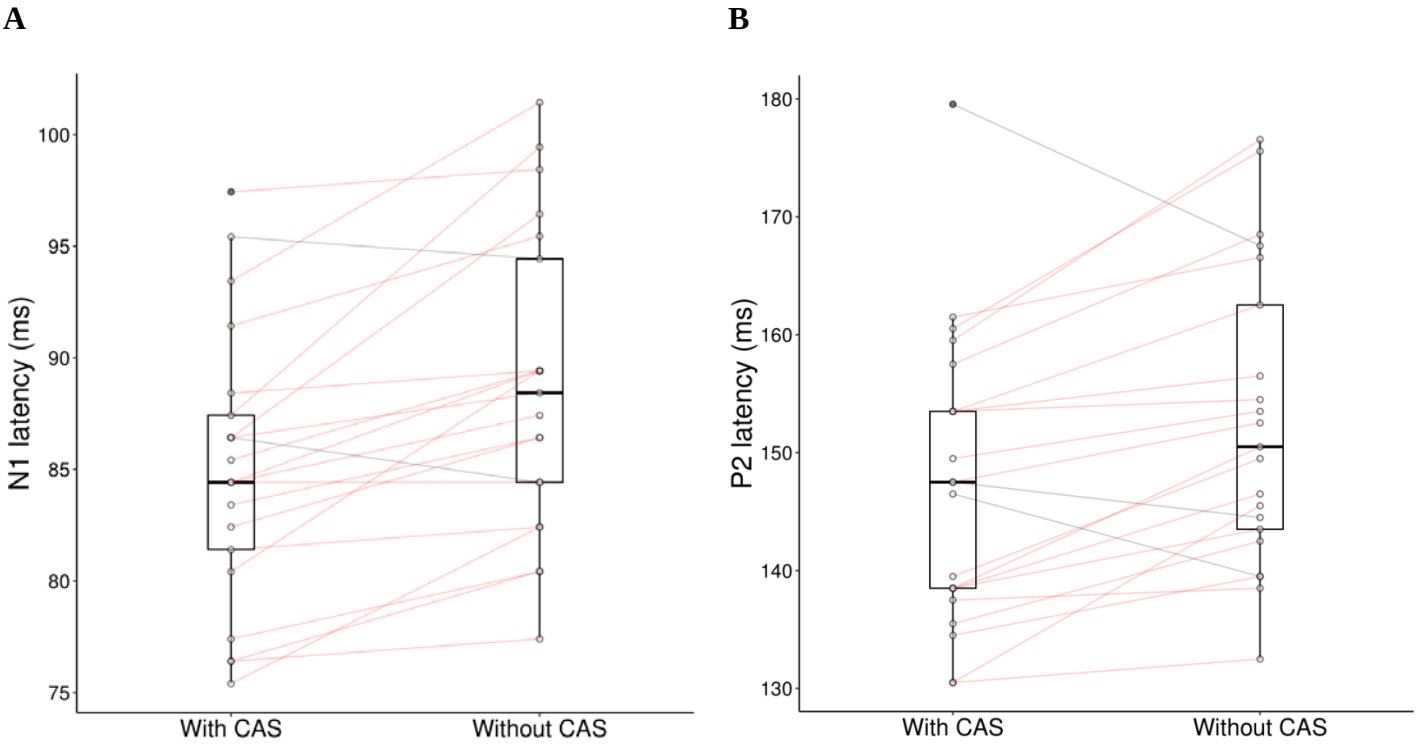

Figure 9. Auditory cortical N1 and P2 latencies with and without contralateral noise. A. N1 latencies were significantly reduced with CAS (RM three-way ANOVA, main effect of CAS: F(1,20) = 22.10, p < 0.001, n_p^2 = 0.52). Red lines show a reduction in N1 latencies with CAS in

19 subjects. **B.** P2 latencies were significantly reduced with CAS (RM three-way ANOVA, main effect of CAS F(1,20) = 22.10, p = 0.003, n_p^2 = 0.37). Red lines show a reduction in P2 latencies with CAS in 18 subjects.

In the control experiment (no behavior, passive presentation of visual and auditory stimuli, n=10), we found a non-significant difference in the amplitude of N1 responses during the baseline and delay periods (N1: F[1,9] = 2.59, p < 0.142, n_p^2 = 0.22). Regarding P2 amplitude, we found a significant reduction during the delay period as compared to baseline (P2: F[1,9] = 8.17, p < 0.019, n_p^2 = 0.48). Figure 10 shows the individual values of N1 and P2 amplitude for the visual working memory and control experiments.

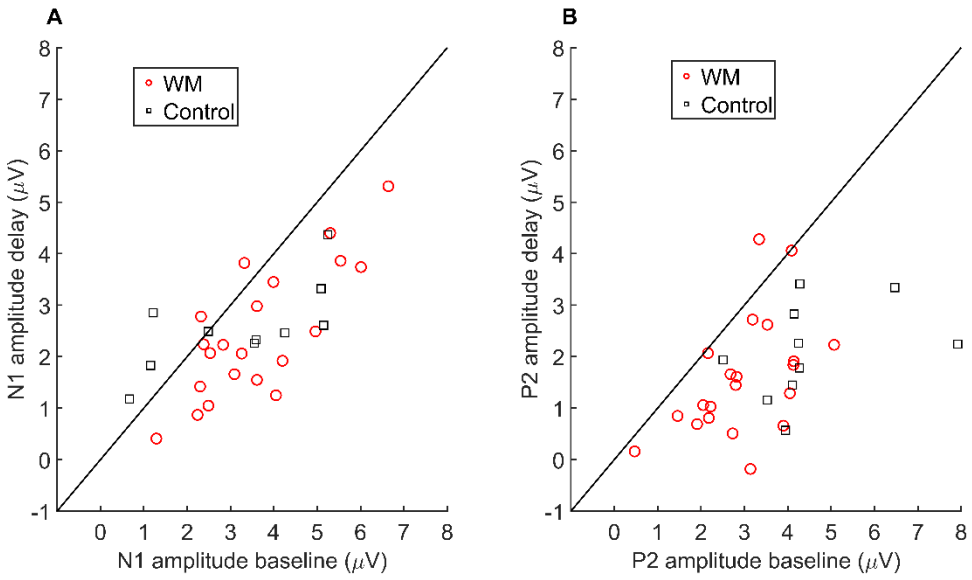

Figure 10. Individual N1 and P2 amplitudes in the baseline and delay periods in the working memory and control experiments. Each symbol represent one subject from the working memory experiments (n=21, red circles) or from the control condition (n=10, black squares). Significant reduction of N1 responses were obtained during the delay period of the

working memory experiment, but not in controls, while P2 was reduced in both conditions (control and working memory experiments).

	ANOVA Comparison	N1	P2
Amplitude	Task period	F[1,20] = 34.61, p < 0.001, n_p^2 = 0.63	F(1,20) = 30.74; p < 0.001, n_p^2 = 0.61
	WM load	F(1,20) = 0.68; p = 0.41, n_p^2 = 0.03	F(1,20) = 0.21; p = 0.64, n_p^2 = 0.01
	CAS	F(1,20) = 2.45; p = 0.13, n_p^2 = 0.11	F(1,20) = 30.77; p < 0.001, n_p^2 = 0.51
	Task period and CAS	F(1,20) = 14.23; p = 0.001, n_p^2 = 0.42	F(1,20) = 1.30; p = 0.26, n_p^2 = 0.06
Latency	Task period	F(1,20) = 2.57; p = 0.12, n_p^2 = 0.11	F(1,20) = 14.43; p = 0.001, n_p^2 = 0.42
	WM load	F(1,20) = 0.30; p = 0.58, n_p^2 = 0.01	F(1,20) = 0.03; p = 0.861, n_p^2 = 0
	CAS	F(1,20) = 22.10; p < 0.001, n_p^2 = 0.52	F(1,20) = 22.10; p = 0.003, n_p^2 = 0.37

Table 2. EEG amplitude and latency results. The table shows N1 and P2 amplitude and latency statistical results compared between baseline and visual WM period, with and without CAS and low and high WM load. All analyses were made using a RM three-way ANOVA. Bonferroni post hoc test of the interaction of task period and CAS in P2 amplitude is showed in the table 1.

CAS effect on DPOAEs

We obtained reliable 2f1-f2 DPOAEs in all subjects, with a mean amplitude of 13.5 dB SPL (SD 4.6), and a range between 4.4 dB SPL and 20.3 dB SPL. The range of frequencies of the recorded DPOAEs was between 1.0 and 1.45 kHz, being the majority around 1 kHz. DPOAE amplitudes were significantly suppressed by the contralateral noise in the baseline (paired t-test, $t_{(20)}$ = 3.04, p = 0.006) and visual working memory period (paired t-test, $t_{(20)}$ = 3.87 p < 0.001),

and in the low (paired t-test, $t_{(20)}$ = 3.25, p =0.004) and high working memory load conditions (paired t-test, $t_{(20)}$ = 3.44, p = 0.003). All statistical DPOAE comparisons between the delay and working memory period were made using two-way repeated measures ANOVA, evaluating the effect of CAS on DPOAE as the main effect. Statistical comparisons between the CAS effects on DPOAE the different conditions are summarized in Table 3. The average CAS suppression on DPOAE amplitudes was significantly larger during the working memory period than during the baseline (Figure 11, DPOAE mean amplitude suppression: baseline period: -0.15 dB (SD = 0.25); delay period: -0.20 dB (SD = 0.25); RM two-way ANOVA, F(1,20) = 5.72, p = 0.03, n_p^2 = 0.22), while non-significant differences were obtained when comparing the external ear canal noise amplitudes between the same conditions (Figure 12, RM two-way ANOVA, F(1,20) = 0.17, p = 0.679, n_p^2 = 0.01). A non-significant difference was obtained when comparing the strength of CAS suppression on DPOAEs between the low and high visual WM load conditions (DPOAE mean amplitude suppression: low WM load: -0.16 dB (SD = 0.24); high WM load: -0.20 dB (SD = 0.27); RM two-way ANOVA, F(1,20) = 0.1, p = 0.32, n_p^2 = 0.05). Figure 13 shows the absolute value of the mean and standard error for the DPOAE suppression by CAS in the low and high working memory load conditions in the baseline and visual working memory period.

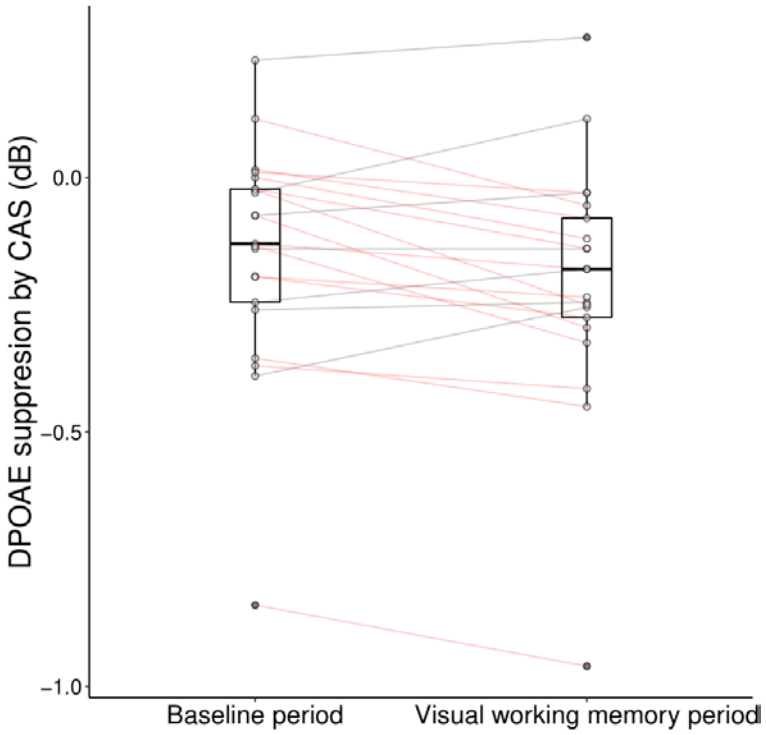

Figure 11. Larger DPOAE amplitude suppression by contralateral noise during the visual working memory period. Boxplot show the median, interquartile range and 95% confidence interval in the baseline and VWM periods, while symbols represent the individual strength of the olivocochlear reflex. Red lines show subjects with CAS suppression of DPOAE amplitudes in the delay interval (n = 14), while grey lines show individuals with opposite effects (n = 7). In average, the olivocochlear reflex strength was stronger during the visual working memory period compared with baseline (RM two-way ANOVA, F(1,20) = 5.72, Bonferroni posthoc test, p = 0.03, n_p^2 = 0.22).

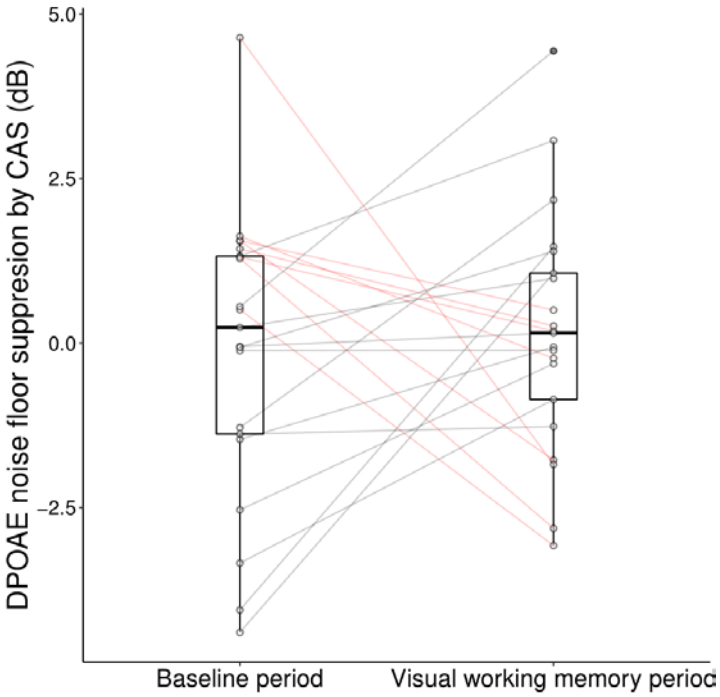

Figure 12. DPOAE noise floor suppression by CAS compared between the baseline and working memory period. No significant effects were found when comparing the DPOAE noise floor suppression by CAS between the baseline and working memory period (RM two-way ANOVA, F(1,20) = 0.17, Bonferroni posthoc test, p = 0.679, n_p^2 = 0.01)

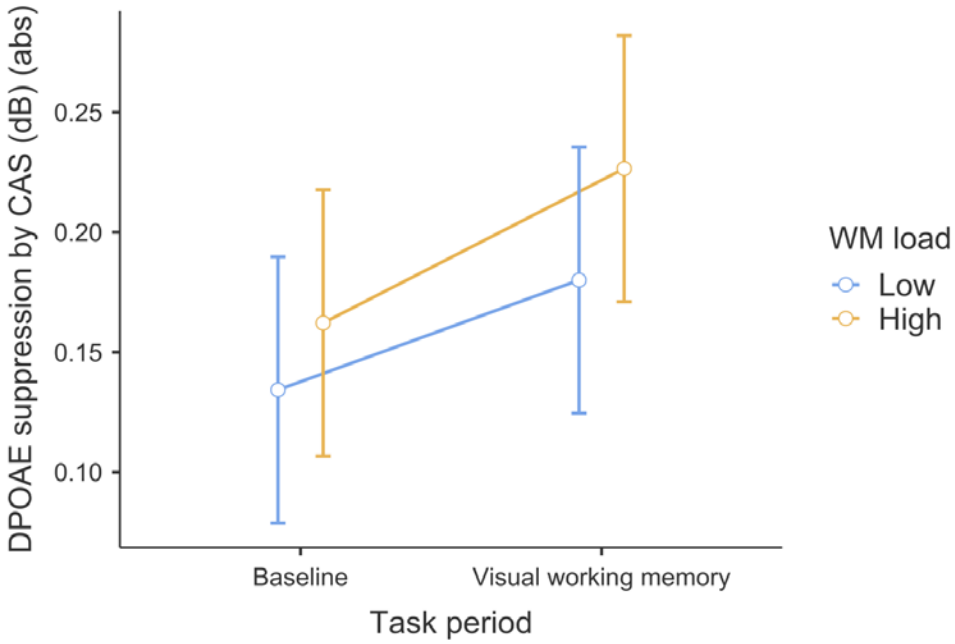

Figure 13. DPOAE suppression by CAS (absolute value) in the low and high working memory load conditions in the baseline and visual working memory period. No significant difference was found between DPOAE suppression by CAS in the low and high WM load (RM two-way ANOVA, F(1,20) = 0.1, p = 0.32, n_p^2 = 0.22). Bar error shows the standar error of the mean.

In the control experiment (n=10) there was no difference when comparing CAS suppression on DPOAE amplitudes between baseline and the working memory period (RM two-way ANOVA, F(1,9) = 1.51, p = 0.250, n_p^2 = 0.14).

Importantly, the cognitive effect on the medial olivocochlear reflex that can be attributable to visual working memory is the difference between the CAS effects on DPOAE between the baseline and delay periods in the control and working memory conditions. Figure 14A shows a significant difference between these measures in the working memory task (n=21) and in the control condition (n=10) (two-tailed t-test, t(29)= -2.107; p=0.04). Figure 14B shows the lack of correlation between the basal amplitude of DPOAE and the difference in the effects of CAS on DPOAE in the working memory and control conditions (Pearson tests, p>0.05).

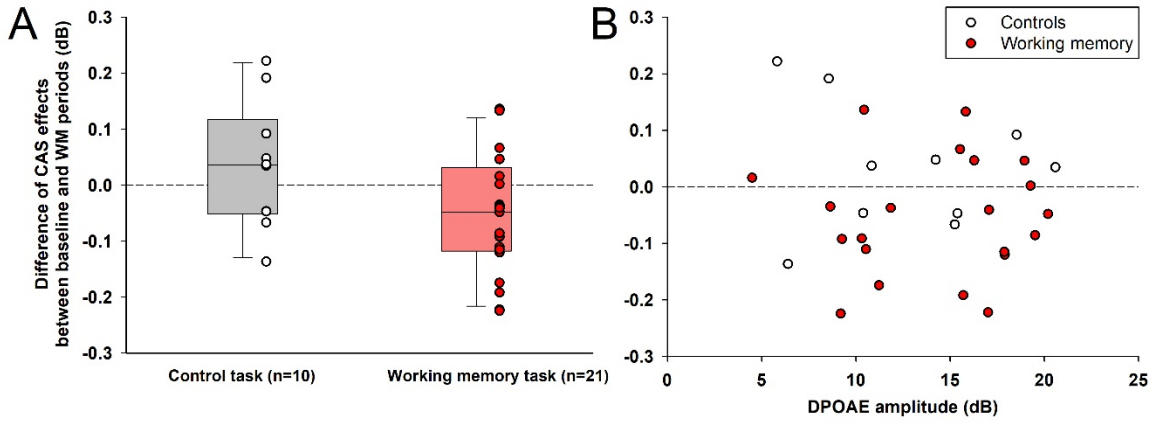

Figure 14. Larger DPOAE amplitude suppression by contralateral noise during the visual working memory task. (A) Boxplots show the median, interquartile range and 95% confidence interval of the difference of CAS effects on DPOAE between baseline and delay periods in the working memory task and in controls. Symbols represent the individual data. The difference of CAS effects on DPOAE in the working memory condition corresponds to -36.6 % of change (more suppression) compared to the basal effect, while for the control condition the change was 8.6% (less suppression). (B) There is no relation between the individual amplitude of DPOAE and the differential CAS effects on DPOAE during the working memory and control conditions.

In order to study the temporal course of the CAS effect on DPOAE, we compared the changes in DPOAE suppression by CAS across conditions between the 0-100 ms and 100-200 ms interval of the epoch. The mean DPOAE suppression by CAS in the 0-100 ms interval was 0.089 dB (SD = 0.26), while the mean DPOAE suppression by CAS in the 100-200 ms interval was 0.26 dB (SD = 0.33), with a significant difference between them (paired t-test, t(20) = -2.09 $p < 0.05$). Neither DPOAE suppression by CAS in the 0-100 ms interval nor in the 100-200 ms interval showed an statistical difference between baseline and visual WM period (0-100 ms interval: RM two-way ANOVA, F(1,20) = 0.021, p = 0.88, $n_p^2 = 0$; 100-200 ms interval: RM two-way ANOVA, F(1,20) = 0.045, p = 0.83, $n_p^2 = 0$).

Correlations between EEG and CAS on DPOAE effects

We explored possible correlations between EEG evoked responses and CAS suppression on DPOAEs. Scatter plots of Figure 15 show non-significant correlations between cortical evoked potentials and the effects of CAS on DPOAE amplitudes (N1: Pearson test, R = 0.28, p = 0.22;

P2: Pearson test, R = 0.17, p = 0.46). Finally, we correlated the individual working memory capacity with the evoked potentials amplitude and CAS effects on the amplitude of DPOAEs. We found a significant correlation between the individual visual WM capacity and P2 amplitude during the VWM period (Figure 16, Pearson correlation, R = -0.69, p < 0.001), while non-significant correlations were obtained for N1 amplitude and DPOAE suppressions by CAS with the individual visual WM capacity (N1: Pearson test, R = 0.075, p = 0.75; DPOAE: Pearson test, R = -0.37, p = 0.01).

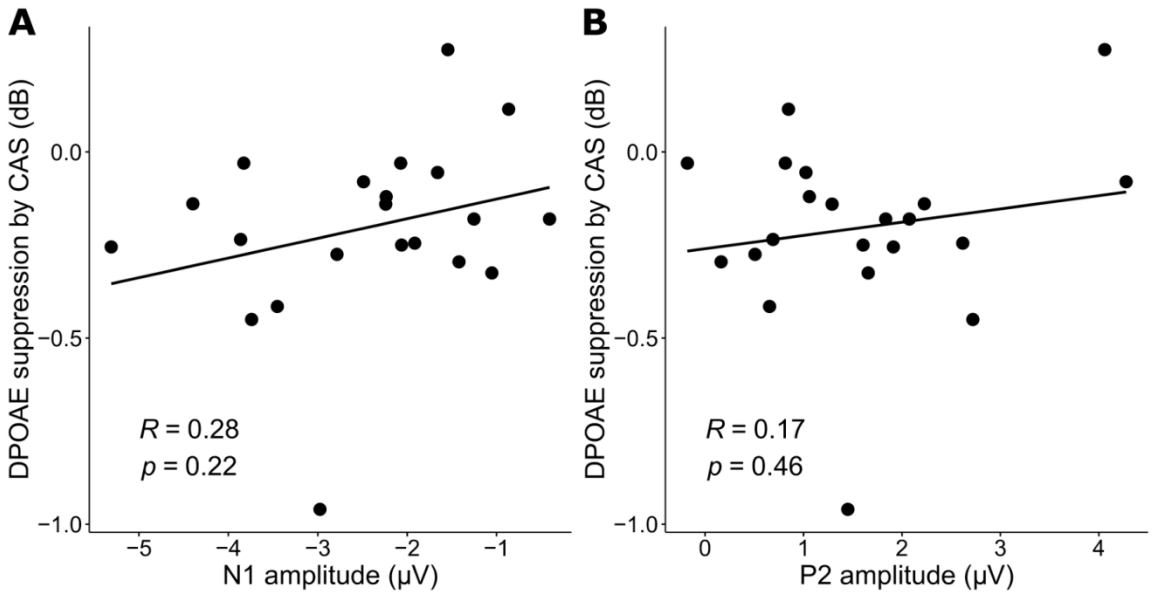

Figure 15. Non-significant correlations between DPOAE amplitude suppression by CAS and N1-P2 amplitudes. (N = 21). Non-significant correlations were obtained between the magnitude of DPOAE amplitude suppression by CAS and N1 amplitudes (Pearson test, R = 0.28, p = 0.22) and P2 amplitudes (Pearson test, R = 0.17, p = 0.46) during the visual working memory period.

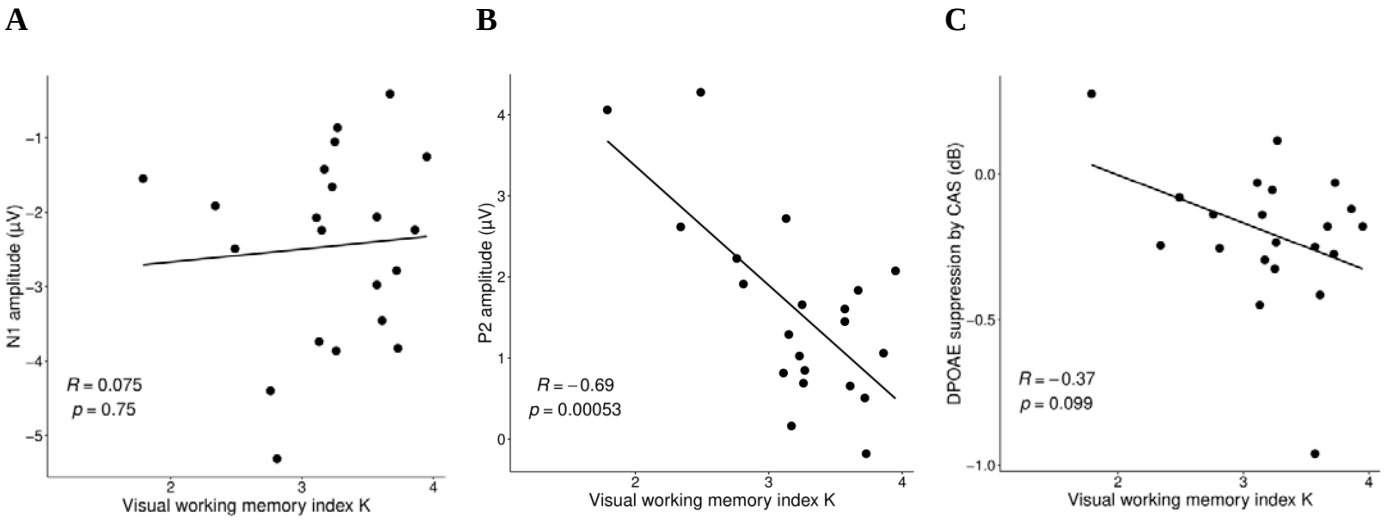

Figure 16. Significant correlation between the amplitude of P2 and the individual visual working memory capacity during the working memory period. (N = 21). **(A)** A non-significant correlation was found between individual N1 amplitude and VWM capacity (Pearson test, R = 0.075, p = 0.75). **(B)** Individuals with higher visual WM capacity have larger reductions of the P2 responses evoked by distracting sounds. (Pearson test, R = -0.69, $p < 0.001$) during the delay period. **(C)** A non-significant correlation was obtained between the individual strength of DPOAE suppression by CAS and the VWM capacity index during the working memory period (Pearson test, R = -0.37, p = 0.01).

DISCUSSION

In this study we present evidence that the strength of the olivocochlear reflex is modulated during the period of visual working memory. Additionally, we show that the changes in P2 amplitude are correlated with the individual VWM capacity. Our findings suggest a common mechanism for suppressing cochlear responses during visual selective attention and visual working memory paradigms.

Behavioral results

Behavioral results showed a significant difference in hit rates and reaction times between low and high visual WM load (figure 3). This was an expected result as the increase in working memory load induce an increase in the difficulty of the task. The contralateral noise did not affect hit rates and reaction times in each WM load condition, so the distraction effect produced by the contralateral noise was probably not enough to disrupt the task in comparision with no contralateral noise condition. This might be due to the fact that the no CAS condition already had auditory distractors (DPOAE eliciting tones), because these two primary tones were presented in all trials.

The average individual working memory capacity obtained in the task was 3.01, which means that an average of 3 items was succesfully maintained in mind by the individuals tested in this study, an average coefficient expected for this type of task for young adults (Isbell et al. 2015). Two individuals probably could have had a better estimate if the maximun working memory capacity was not restricted to 4, and for this reason is probably that the average working memory capacity is in an small amount understimated.

EEG auditory evoked potentials (N1-P2)

Our results showed an amplitude reduction of cortical auditory evoked potentials (N1 and P2) during the visual working memory period. Previous studies found mixed results: similar to our findings, Simon et al. (2016) and Tusch et al. (2016) found reduced auditory N1 responses during visual WM, whereas Regenbogen et al. (2012) and Valtonen et al. (2003) found an increase in N1-P2 and in N1m amplitudes during visual WM, respectively, while others authors found no modulation (Otten et al. 2000; Zhang et al. 2006). Different experimental paradigms, stimuli and manipulations could account for these different results. Besides the influence of visual working memory, another possibility to explain the amplitude reduction of N1 and P2 responses could arise from their dependence to the inter-stimulus-interval (ISI). It is well known that the amplitudes of N1 and P2 increase as the ISI becomes longer (Picton 2013). In our case, the ISI between baseline and delay period was 950 ms, while between trials was 2350 ms. According to Pereira et al. (2014), an amplitude reduction of almost 50% can be observed when comparing N1-P2 amplitudes obtained with ISI of 1 and 3 seconds. Another explanation may arise from the individual variability observed in the olivocochlear activity (evidenced by CAS effects on DPOAE amplitudes, Figure 10), which could be influencing EEG responses. Therefore, although we found a reduction of N1 and P2 during the working memory period, these results should be considered carefully as besides working memory, many other factors could be influencing the amplitude of N1 and P2 responses.

We did not find significant results in N1 or P2 amplitude changes between two and four squares VWM load conditions (Figure 2B). A speculative explanation for this result is that the different working memory load conditions that we used (two or four items) were similar, as our subjects had an average working memory capacity of three items, so the difference in average between both conditions was in practice one item and not two items. For future works, we

suggest to expand the difference between the VWM load conditions (for example using 1 and 5 squares), that might help to show significant differences between high and low VWM loads. Increasing the number of squares beyond the working memory capacity would increase the concentration and arousal needed to perform the task while maintaining the WM load, and this could help to disentangle which of two aspect of cognition (WM or arousal) is related to top-down mechanisms.

The contralateral noise showed to increase P2 amplitude but only in the baseline period (figure 6 and 7). The CAS was delivered at the same time of the primary tones, and it is possible that an increment in the general level of sound is responsible for the increase in P2 amplitude, as is it well documented that an increase in the sound level increases the amplitude of the early auditory evoked potentials. The amplitude reduction (because of WM load or the inter and intra trial difference) produced in the visual WM period might surpass the augmentation related to the increase in sound level, and that could be a reason why there is no difference in the P2 amplitude with and without CAS in the visual WM period. It is possible that P2 could be involved in the computation of more complex aspects of the sound (or be more sensitive by), as the complexity of the sound increases with the addition of noise, and this could be a reason why N1 amplitude was not modulated by the contralateral noise.

P2 latencies were significantly reduced in the visual working memory period only. Extensive evidence have shown that a reduction in latency is coupled with an increment in amplitude when the sound level is increased (Picton 2013), but in our results, there was a reduction in amplitude in the visual working memory period. One possible explanation is that when a distracting sound is predictable, as was in our task, the brain can process it more rapidly to avoid distraction. There was also a tendency in the same trend in N1 latency, but as did not show statistically

significance, it is possible that the reduction in latency has more impact for distraction only in later stages of processing. This hypothesis can also be applied if the difference in intra and inter trial interval is the underlying explanation for the reduction in amplitude in P2, as the habituation mechanism has also been related to a reduction in the processing of irrelevant information (Takeuchi et al. 2017).

The contralateral noise induced a reduction in N1 and P2 latencies in the task, a result that can be expected (as was discussed for the increase in amplitude in P2) when the sound level is incremented. The effect showed to be more significant in N1 than P2 latency, the opposite of amplitude, where the contralateral noise modulted P2 amplitude.

We find a significant reduction in P2 amplitude between the baseline and delay period in the control experiment, at similar percentage of reduction as in the visual working memory task (54% vs 46%, respectively). This result show that the reduction of P2 is most probably due to the effect of the inter and intra trial difference in the the sound stimulus used in each trial. In the other hand, N1 amplitude did not show a significant effect reduction between the baseline and delay period in the control experiment, and showed and average reduction of 20%. The reduction in N1 amplitude in the visual working memory task was statistically signiticant and in the order of 32%. This result shows that N1 amplitude could be partially modulated by visual working memory.

Correlations

We found a significant correlation between the individual VWM capacity and P2 amplitudes during the WM period (Figure 16). Sörqvist et al. (2012), showed that the amplitude changes of auditory evoked midbrain responses (ABR wave V) between high and low WM load, correlated with the individual visual-verbal WM capacity. Together, our results, and Sörqvist et

al. (2012) are in agreement with the evidence showing that the capacity of filtering distracting stimuli can play an important role on the individual WM capacity (Gaspar et al. 2016; Sörqvist et al. 2012; Vogel et al. 2005). Amplitude and latency effects show that the effect of the visual WM period had stronger effects on P2 than on N1 responses. In a similar manner, different effects in N1 and P2 amplitudes have been also observed during sleep and aging (Crowley and Colrain 2004). A possible explanation for the differential effects on N1 and P2 could be related to the evidence supporting the notion that N1 and P2 responses are generated in different regions of the brain: the neural generators of N1 arise from the primary auditory cortex, frontal lobe and midbrain, while P2 has been related to the thalamus-reticular activating system (Bishop et al. 2007). In this context, P2 function has been related to the gate into attention and counciousness of sensory stimulus (Näätänen 1992), N1 showed to be more related with automatic processes of change detection, as the mismatch negativity (Näätänen et al. 2007).

Cognitive effects on the cochlear receptor

At the cochlear level, we found that the average DPOAE amplitude suppression by CAS increased during the visual working memory period. The contralateral acoustic stimulation activates the olivocochlear reflex, a brainstem circuit that reduces the cochlear gain (De Venecia et al. 2005; Lopez-Poveda et al. 2017). The olivocochlear reflex strength was quantified in our data by measuring DPOAE amplitude changes produced by CAS. Although the magnitude of the effects that we obtained with CAS on DPOAE is relatively small (< 1 dB), it is important to note that the efferent effect studied with CAS on DPOAE may underestimate the magnitude of the olivocochlear reflex, as it is known that electrophysiological changes on cochlear potentials by electrical activation of the medial olivocochlear efferent system are larger than DPOAE changes (Puria et al. 1996).

Importantly, Perrot and colleagues showed that the electrical stimulation of the auditory cortex can modulate the amplitude of otoacoustic emissions, evidencing a corticofugal mechanisms on the cochlear receptor in humans (Perrot et al. 2006). In addition, a previous study in selective attention found a significant increase of the suppressive effects on click-evoked otoacoustic emissions produced by contralateral noise stimulation during a visual attention period (Ferber-Viart et al. 1995). Here, we found that during visual working memory, the majority of the individuals had a stronger activation of the olivocochlear reflex (Figure 11). From these results, we propose that the corticofugal mechanisms can increase the efferent suppression of cochlear responses to auditory distractors during a visual working memory state. Therefore, taking the findings from preceding works and the present results, we can suggest that the olivocochlear reflex can be modulated by different cognitive tasks, including selective attention and working memory.

Previous studies assessing visual selective attention effects on DPOAEs have shown mixed results. While some studies have shown a relative increase of DPOAE amplitudes when subjects attended to a visual task compared with an auditory task (Smith et al. 2012; Srinivasan et al. 2012; Srinivasan et al. 2014), others authors found a reduction of DPOAE amplitudes by visual selective attention (Wittekindt et al. 2014). In our case, at the individual level, we found a reduction of DPOAE in the majority of the cases (n=14), which contributed to the main effect. However, in a subset of individuals (n=7), we found opposite effects, showing that similar to selective attention paradigms, the olivocochlear activation during visual working memory is variable among subjects. This trend was similar to the obtained by Wittekindt et al. 2014, where in 16 of 23 sujects the DPOAE amplitude was reduced in the visual attention condition compared to auditory selective attention. The group of participant who had reduction in DPOAE responses

had no difference in DPOAE basal level, average DPOAE suppresion by CAS, age or EEG responses with the group with increases DPOAE responses (data not shown), so further research is needed to clarify the factors that contribute to this difference in response.

Measurements of DPOAE during behavioral tasks

Movements and probe displacement in the external ear canal have been proposed as important issues that may affect DPOAE results in behavioral paradigms (Francis et al., 2018). Importantly, here we compared the DPOAEs suppresion by CAS obtained in the baseline period with DPOAEs in the delay period, comparing changes in DPOAE within each trial (Wittekindt et al. 2014). This approach avoided possible slow drifts in DPOAE amplitudes that can occur because of small changes in the probe position inside the ear over time (Francis et al. 2018). In addition, we found non-significant amplitude differences when comparing the effects of CAS on the noise recorded from the external ear canal, showing that the DPOAE effects observed in Figure 3 are most probably originated from an activation of the olivocochlear system.

Besides that there was no difference in DPOAE suppresion by CAS between low and high WM load, from the figure 12 it is possible to observe a trend towars an increase in DPOAE suppression with high WM load. As discussed with EEG responses, the average WM capacity of our individuals was 3, and probably the difference between low (2 squares) and high (4 squares, but 3 in practice) was not enough to show a statiscally significant effect. Subsequent studies should increase the number of participant to test this idea.

Control experiment

The control experiment support the result obtained by the visual working memory task, as no modulation on DPOAE amplitude suppresion by CAS between the baseline and visual working memory period was found. We found no relation between the individual DPOAE amplitude and

the effects of visual working memory in DPOAE suppression by CAS (Figure 14B). These results suggest that, similar to physiological experiments with auditory-cortex electrical microstimulation (Dragicevic et al., 2015), during the visual working memory condition there is a modulation of the medial olivocochlear reflex strength, independently of the modulation of cochlear sensitivity.

Middle ear muscle activation during cognitive tasks

The reflex activation of the MEMs (stapedius and tensor tympani muscles) is well documented as a protective mechanism for high intensity sounds, usually above 70 dB for noise and above 90 dB for pure tones (Liberman and Guinan 1998). In our experiments we used CAS at 60 dB, and despite we did not measure MEM activation during the working memory task, it is very unlikely that a reflexive activation of MEMs by high intensity sounds contributes to the suppressive effects on DPOAE. However, a cognitive top-down activation of MEMs cannot be ruled out as an alternative mechanism to suppress peripheral responses. In this line, selective attention experiments in medial olivocochlear knock-out (Terreros et al. 2016) suggested a cognitive activation of MEMs. The idea of a combined activation of auditory efferents and MEMs by top-down cognition should considered an alternative model in future experiments.

Relationship between DPOAE and EEG responses

Our results showed that DPOAE amplitude changes were not correlated with changes in cortical responses (figure 15), neither with individual VWM capacity (Figure 16). A similar result was obtained by Wittekindt et al. (2014) in a crossmodal auditory-visual selective attention task in which they found no correlation between EEG and cochlear measures. The lack of correlation could be explained by the different roles that the cochlear amplifier and N1-P2 responses have in the sound processing, as DPOAEs are a subproduct of a mechanism related to the increase in the

signal to noise ratio of the signal, while N1-P2 responses are related with the processing of more complex aspect of the signal as discussed above. One important limitation of the present work and shared by Wittekindt et al. (2014) is that both studies were developed to study the amplitude of DPOAEs in the time domain, but not in the frequency domain. Recently, we showed that cortical and cochlear low-frequency oscillations (in the frequency range of delta and theta bands) increased their amplitudes when the subjects are engaged in an auditory-visual selective attention task (Dragicevic et al. 2019). Unfortunately, the present work was designed with discrete tones, which impedes the analysis of the envelope of a continuous DPOAE signal in the frequency domain. Future studies in working memory and otoacoustic emissions should address cochlear and cortical oscillatory mechanisms.

The auditory efferent network in cognitive demanding tasks

The neuroanatomical pathways of the olivocochlear reflex are located in the brainstem, including auditory nerve, cochlear nucleus and medial olivocochlear neurons (De Venecia et al. 2005). In addition, physiological studies have shown that the olivocochlear reflex can be modulated by auditory cortex descending projections (Dragicevic et al. 2015; Aedo et al., 2016). Interestingly, a recent neuroanatomical study showed that the inferior colliculus receives direct connections from non-auditory regions of the cortex, like visual, somatosensory, motor, and prefrontal cortices (Olthof et al. 2019). In this line, we propose a more general cognitive function for the auditory efferent system, which is to reduce or filter cochlear responses during highly demanding cognitive tasks, including selective attention and working memory, by activation of top-down cortical networks from the frontal cortex and other non-auditory regions to the cochlear receptor (Figure 17).

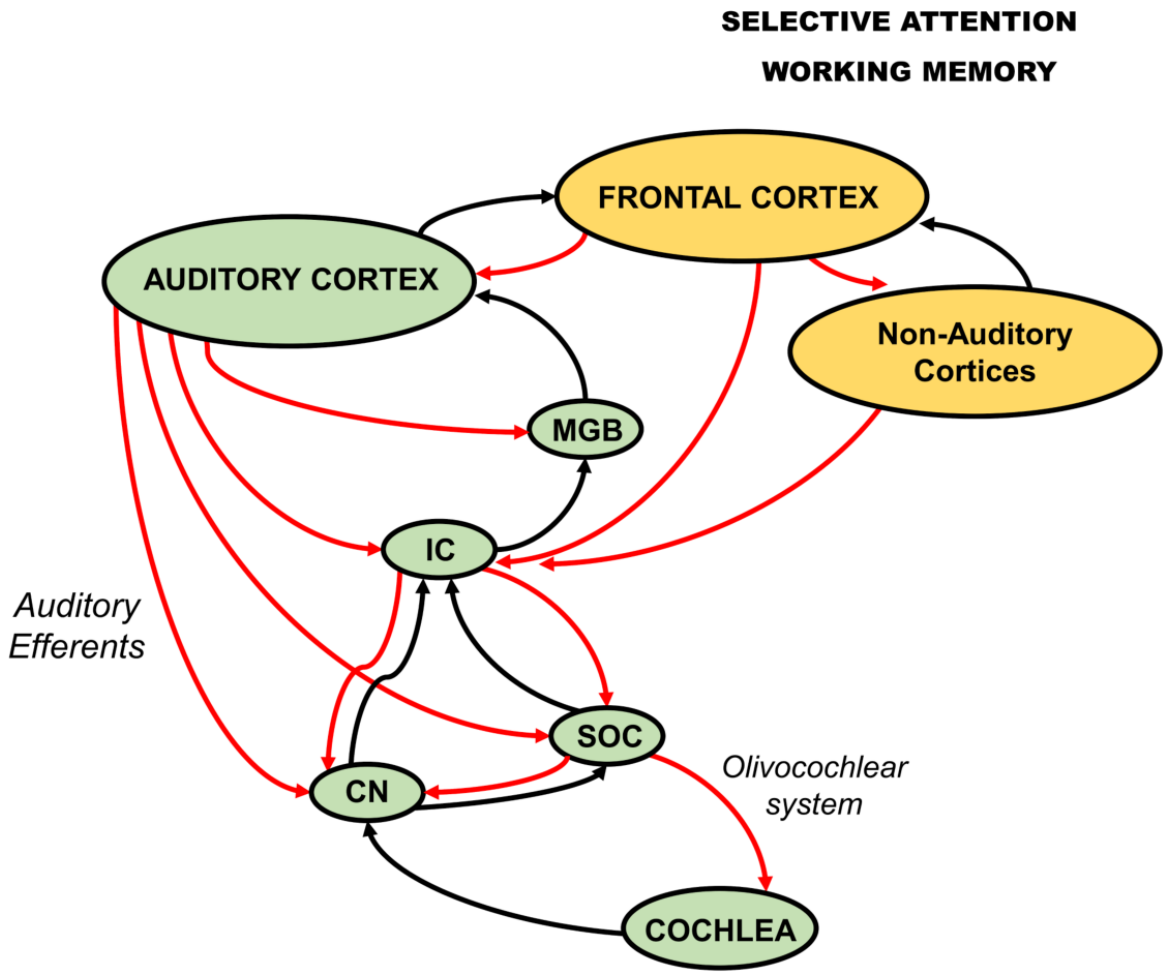

Figure 17. Diagram of top-down networks from frontal cortex to the cochlear receptor. Different pathways of the efferent auditory system from the auditory cortex to the cochlea. Modified with permission from Terreros and Delano 2015. It is important to highlight that a recent study in rats described direct pathways from prefrontal cortex and non-auditory cortices to the inferior colliculus (Olthof et al. 2019).

Conclusion and future work

Here we show that the strength of olivocochlear reflex is modulated when visual objects are kept in mind. In addition, we show evidence that N1 amplitude responses could be modulated

by visual working memory and that the individual VWM capacity correlated with the amplitude of P2 responses elicited during the visual working memory period. These results expand the role of the auditory efferent system to working memory mechanisms, showing that selective attention and working memory can share similar mechanisms to filter cochlear responses probably through olivocochlear neurons. In future works we suggest expanding the difference between working memory load in the task, using a condition with one item would probably lead increase the chance to get a difference in the responses. In addittion, a large intertrial interval could have benefits helping to obtain a baseline period reduced arousal. As discussed above, the frequency domain of the otoacustic emission signal the could be an intesting are to further explore in visual working memory tasks. Finally, using an estimate of working memory capacity obtained with a independent task and, for example a complex span task, could give better estimate than a sensory-specific (visual in our case) working memory capacity.

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