Neuroscience

# Subcortical correlates of consciousness with human single neuron recordings

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## Abstract

Subcortical brain structures such as the basal ganglia or the thalamus are involved in regulating motor and cognitive behavior. However, their contribution to perceptual consciousness is still unclear, due to the inherent difficulties of recording subcortical neuronal activity in humans. Here, we asked neurological patients undergoing surgery for deep brain stimulation to detect weak vibrotactile stimuli applied on their hand while recording single neuron activity from the tip of a microelectrode. We isolated putative single neurons in the subthalamic nucleus and thalamus. A significant proportion of neurons modulated their activity while participants were expecting a stimulus. We isolated a subset of neurons for which we had sufficiently good behavior to contrast neuronal activity between detected and undetected stimuli. We found that the firing rate of 23% of these neurons differed between detected and undetected stimuli. Our results provide direct neurophysiological evidence of the involvement of subcortical structures in for the detection of vibrotactile stimuli, thereby calling for a less cortico-centric view of the neural correlates of consciousness.

### eLife assessment

This **important** study reports human single-neuron recordings in subcortical structures while participants performed a tactile detection task around the perceptual threshold. The study and the analyses are well conducted and provide **solid** evidence that the thalamus and the subthalamic nucleus contain neurons whose activity correlates with the task, with stimulus presentation, and even with whether the stimulation is consciously detected or not. The study will be relevant for researchers interested in the role of subcortical structures in tactile perception and the neural correlates of consciousness.

# Introduction

Current methods to investigate the *neural correlates of consciousness* aim at contrasting the neural activity associated with different percepts under constant sensory stimulation to identify the minimal set of neuronal events sufficient for a specific conscious percept to occur (Koch et al., 2016; Seth et al., 2022). Typically, this involves asking participants to report whether a stimulus with an intensity around detection threshold is present or not. Taking advantage of the wealth of invasive electrophysiology recordings available, researchers have documented such correlates with detection tasks in rodents (e.g., Schmack et al., 2021), birds (Nieder et al., 2020) and non-human primates (e.g., Leopold & Logothetis 1996; de Lafuente & Romo, 2005). However, the use of animal models to study consciousness raises specific ethical concerns (e.g., Mazor et al., 2023), and requires interpreting behavioral responses with caution (Birch et al., 2022). Research into the neural correlates of consciousness in human volunteers is enriched by the analysis of fine-grained subjective reports to rule out various confounds (e.g attention, memory, report), but suffers from less spatially and temporally resolved physiological measurements. Indeed, only very few studies have found such correlates at the single neuron level (Fried et al., 1997; Quiroga et al., 2008; Reber et al., 2017; Gelbard-Sagiv et al., 2018; Pereira et al., 2021) and only in cortical regions. The role of subcortical structures for perceptual consciousness is theoretically relevant (Seth et al., 2022; Dehaene & Changeux, 2011; Ward, 2013; Schiff et al., 2008; Aru et al., 2020) with some empirical support from detection studies in non-human primates (Vazquez et al., 2012, 2013; Hagens et al., 2014; Tauste Campo et al., 2019), as well as functional imaging or local field potentials in humans (Levinson et al., 2021; Kronemer et al., 2022). Nonetheless, it remains unknown how the firing rate of subcortical neurons changes when a stimulus is consciously perceived. Here, we recorded individual neurons from the subthalamic nucleus (STN) and thalamus of human participants during 36 deep brain stimulation surgeries. Participants detected vibrotactile stimuli provided at the perceptual threshold and we tested how neurons in both subcortical structures were modulated by the task, the onset of the stimulus or the detection or not of the stimulus.

# Results

## Task and behavior

Deep brain stimulation surgeries provide a unique opportunity to record the activity of single neurons in subcortical structures of the human brain. Microelectrode recordings are performed routinely after patients are awakened from anesthesia, to allow electrophysiologists and neurosurgeons to identify the target brain structure along the planned trajectory (**Figures 1B**, S1). During this procedure, we attached a vibrotactile stimulator to the palm of the hand contralateral to the microelectrode recordings and estimated the stimulus intensity corresponding to participants' individual tactile detection threshold. Once stable neuronal activity could be recorded in the target brain region (STN or thalamus), we proceeded to the main experiment, which comprised one or two sessions of 71 trials (total: 48 sessions). Each trial started with an audio "go" cue, followed by a vibrotactile stimulus applied at any time between 0.5 s and 2.5 s after the end of the cue (i.e. stimulation window), except for 20% of catch trials in which no stimulus was applied (**Figure 1A**). After a random delay ranging from 0.5 to 1 s, a "respond" cue was played, prompting participants to verbally report whether they felt a vibration or not. Therefore, none of the reported analyses are confounded by motor responses. Using a staircase procedure, the stimulus intensity was kept around the detection threshold over the whole experiment. When possible, participants were trained to perform the task prior to the surgery.

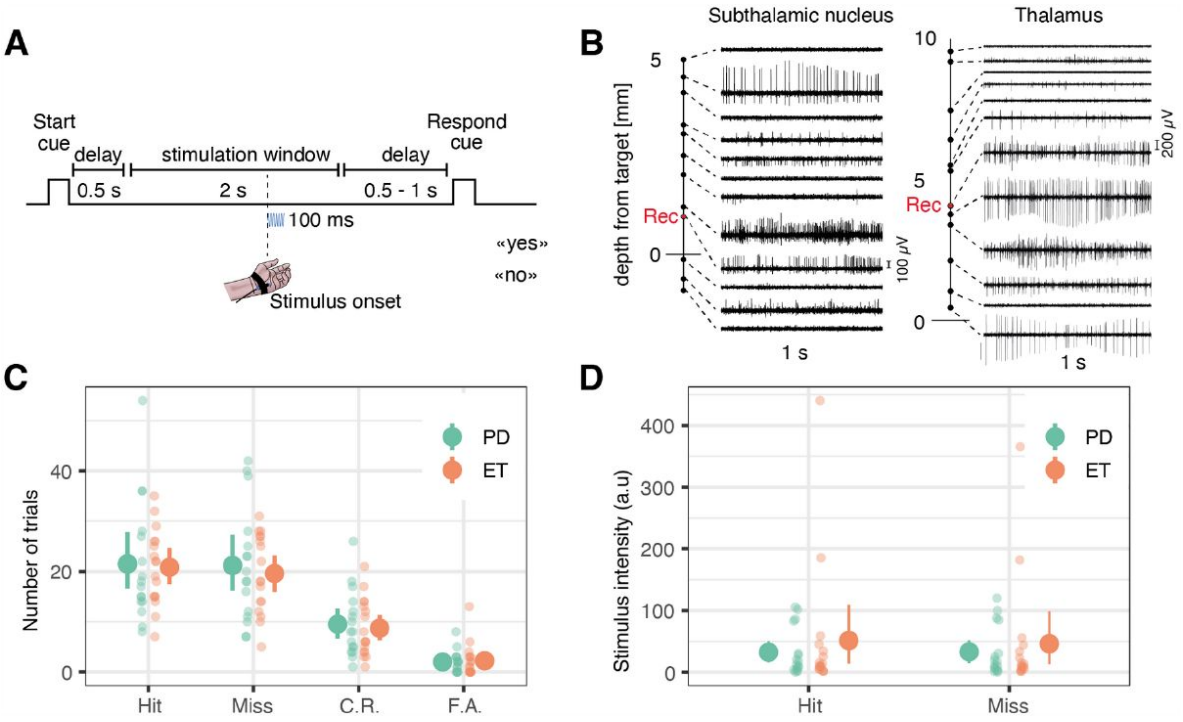



**Figure 1.**

**Task and behavior.**

**A**. Task timeline. Each trial started with an auditory start cue, followed by a 0.5 s delay. Next, the stimulus could occur anytime during a 2 s stimulation window. After a variable 0.5 to 1 s delay, a response cue prompted patients to answer whether or not they detected the stimulus. **B**. Two example sets of 1 s long microelectrode recordings along the surgical tract showing specific firing for the subthalamic nucleus (left) and the motor thalamus (right). The depth at which the research data was collected is represented as a red dot (see Supplementary Figure 1 for anatomical correspondence). **C**. Number of hits, misses, correct rejections (C.R.), and false alarms (F.A.) collected during the main experiment. **D**. Averages of the absolute vibrotactile intensity in hits and misses in arbitrary units (values cannot be compared between participants). In panels C and D, each small dot represents a participant with Parkinson's Disease (PD, in green) or essential tremor (ET, in orange). Big dots represent averages; error bars represent 95% confidence intervals.

When analyzing tactile perception, we ensured that our results were not contaminated with spurious behavior (e.g. fluctuation of attention and arousal due to the surgical procedure). We excluded specific series of trials from analyses based on objective criteria and focused on trials where hits and misses occurred in commensurate proportions (see methods). This procedure led us to keep 36 sessions out of 48 with a mean of 24.0 [95% confidence interval = 22.0, 25.9] hit trials and 22.7 [20.8, 24.5] miss trials. Permutation tests at the single-participant level indicated that detected and missed stimuli were of similar intensity except in 5 sessions for which the intensity of detected stimuli was higher on average. Likewise, detected and missed stimuli had similar onsets, except in 1 session for whom stimuli with late onsets were predominantly missed, and in 2 sessions for whom stimuli with early onsets were predominantly missed. The hit rate was comparable between participants with Parkinson's disease (0.51 [0.49, 0.53]) and essential tremor (0.52 [0.51, 0.53], Wilcoxon rank sum test: W = 114.5, p = 0.45). Catch trials were separated into 9.1 [8.1 10.1] correct rejections and 2.1 [1.7, 2.6] false alarms, with an equivalent false alarm rate between participants with Parkinson's disease (0.24 [0.19, 0.28]) and essential tremor (0.24 [0.18, 0.30], Wilcoxon rank sum test: W = 145, p = 0.76). Intraoperative behavior was similar to the behavior observed during the training session and similar to what we found recently in a cohort of healthy participants using the same task (Pereira et al., 2021).

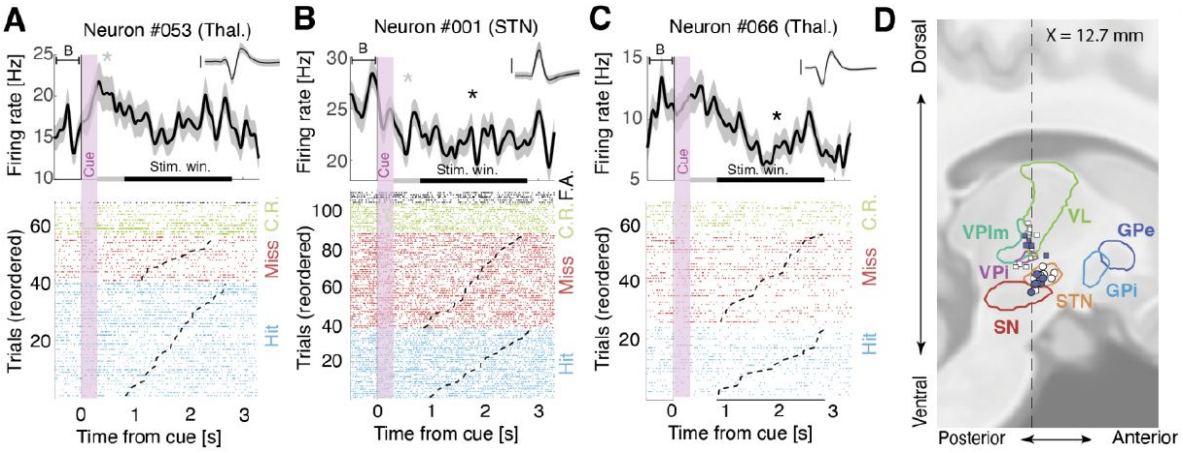
## Neuronal firing was modulated by the task

We performed a total of 48 (STN: 25, Thal: 23) successful microelectrode recording sessions during 36 surgeries for deep brain stimulation electrode implantation. We isolated 50 putative single neurons (STN: 26, Thal: 24) according to spike sorting metrics (Figure S2A-G). We ensured that all neurons showed stable spike amplitudes during the recording (Figure S2H-J). We also ensured that for every analysis, a minimum of 20 trials per condition were kept after removing artifacts. First, we looked for cue-selective neurons that modulate their firing rate during the 500 ms delay following the end of the "go" cue, compared to a 500 ms pre-cue baseline period. There were 8 / 44 (18 %) cue-selective neurons (**Figure 2A**; 6 neurons were removed from the analysis due to an insufficient number of trials). We confirmed that these 8 cue-selective neurons could not have been obtained by chance by comparing this number to a null distribution obtained by permuting trial labels 1000 times (permutation test: $p < 0.001$). The proportion of cue-selective neurons was not significantly different in the STN (21%) and thalamus (15%; difference: $p = 0.31$, permutation test) and 6 out of 8 neurons showed a decrease in firing rate compared to the pre-cue baseline (Binomial test: $p = 0.145$).

Next, we investigated how many neurons showed task-selective modulations by comparing firing rates during the 2 s stimulation window to the 500 ms pre-cue baseline, indicating a modulation of their firing rate when a stimulus is expected. There were 9 / 44 (20 %) task-selective neurons (permutation test: $p < 0.001$) with a similar proportion in the STN (20 %) and thalamus (21 %; binomial test: $p = 0.91$; **Figure 2B-D**). Interestingly, 8 out of 9 neurons decreased their firing rate relative to the pre-cue baseline (Binomial test: $p = 0.020$). In both regions, a significant proportion (44 %; permutation test: $p < 0.001$) of the task-selective neurons were also cue-selective, modulating their firing rate before any sensory stimulation necessary for a decision occurred. Therefore, these cue- and task-selective neurons are unlikely to be involved in decision-related action selection or cancellation (15,16) but should be involved in the detection task *per se*.

## Neuronal firing was modulated by the stimulus

We then searched for neurons that modulate their firing rate after the stimulus onset compared to a 300 ms pre-stimulus baseline while correcting for possible drifts in the firing rate during the trial (see methods). We found 8 / 37 such stimulus-selective neurons (22%, permutation test: $p = 0.011$; **Figure 3A-D**; 13 neurons were removed due to an insufficient number of trials), with 29% in the STN and 11% in the thalamus (difference: binomial test: $p = 0.11$). These differences occurred 210 ms ± 30 after the stimulus onset, lasted for an average of 130 ms ± 30, and 7 out of 8 neurons




## Figure 2.

### Representative cue- and task-responsive neurons in distinct patients.

**A-C**. Upper panels: firing rates time-locked to the onset of a trial (300 ms long auditory cue; vertical purple shade), compared to a 500 ms pre-cue baseline ("B"). Two significance windows were tested: the post-cue window (500 ms after cue offset; grey horizontal bar; cue-selective neurons) or the stimulation window (800 ms to 2800 ms post-cue; black horizontal bar; task-selective neurons). Asterisks represent statistical significance ($p < 0.05$). Shaded areas indicate bootstrapped standard errors. Inset: corresponding action potentials (shaded area indicates standard deviation; vertical bar corresponds to 100 μV). Lower panels: raster plot with trials sorted by stimulus onset (dashed lines) and type: hits (blue), misses (red), correct rejections (C.R.; green), and false alarms (F.A.; black). **A**. Cue-selective neuron in the thalamus. **B**. Cue- and task-selective neurons in the STN. **C**. Task-selective neuron in the thalamus. **D**. Sagittal view of recording locations for thalamic (squares) and subthalamic (circles) targets (see Figure S3A for a coronal view). Filled circles or squares are cue/task-selective neurons. Legend: VL: ventral lateral thalamus, VPlm: ventral posterior lateral and medial thalamus, VPi: ventral posterior inferior thalamus, STN: subthalamic nucleus, SN: substentia nigra, GPi/e: globus pallidus internalis / externalis,

showed a decrease in firing rate after the stimulus onset (Binomial test: p = 0.020). These results show that subthalamic and thalamic neurons are modulated by stimulus onset, irrespective of whether it was reported or not, even though no immediate motor response was required.

### Neuronal firing was modulated by tactile perception

Having identified subcortical neurons that were cue-, task-or stimulus-selective, we next sought to assess the role of these structures in conscious detection by comparing firing rates time-locked to detected vs missed stimuli. Of the 50 neurons recorded, 35 were associated with periods of high-quality behavior, allowing us to assume tactile stimulation at the perceptual threshold. We found 8 neurons (23 %) showing a significant difference after stimulus onset (permutation test: p = 0.0020; **Figure 4A-D**). Each neuron was found in a different participant. The proportion of these perception-selective neurons was similar in the STN (27 %) and the thalamus (20 %; difference: p = 0.529; permutation test). These differences in firing rates occurred 160 ms ± 30 after the stimulus onset and lasted for an average of 90 ms ± 10. We note that, 6 out of 8 neurons had higher firing rates for missed trials than hit trials, although this proportion was not significant (binomial test: p = 0.145). None of the aforementioned neurons showed sustained differences between the highest and lowest stimulus amplitudes nor between early and late stimulus onset within the 2 s stimulus window (**Figure 5**). Our control analyses confirm that our results do not stem from slight differences in stimulus amplitudes due to the staircase procedure or spurious differences induced by the start or response cues. Qualitatively, we found very little overlap between task-, stimulus- and perception-selective neurons (Figure S4). This result suggests that neurons in these two subcortical structures have mostly different functional roles. We also found no clear indication that neurons with a beta-band oscillatory component were more or less selective.

## Discussion

The importance of cortico-subcortical loops for physiological and cognitive functions is well-established (Shepherd & Yamawaki, 2021). Yet, while the role of subcortical structures in perceptual consciousness is largely acknowledged (Dehaene & Changeux, 2011; Koch et al., 2016; Ward, 2013; Aru et al., 2020; Shepherd & Yamawaki, 2021), it remains poorly described in humans. This limit is likely due to the difficulty of recording subcortical activity in awake humans capable of providing conscious reports under controlled experimental conditions. We report the first intraoperative recordings of subcortical neurons in awake individuals during a detection task. By imposing a delay between the end of the tactile stimulation window and the subjective report, we ensured that neuronal responses reflected stimulus detection and not mere motor responses. In addition, because stimuli were applied on the palm, we asked participants to provide detection responses orally to avoid confounding neural activity related to sensory and motor processes of the upper limb. Our main result is that the activity of subcortical neurons co-varies with subjective reports following the presentation of detected vs missed tactile stimuli. This result confirms that the neuronal underpinnings of tactile detection can be observed at the scale of single neurons in humans (Fried et al., 1997; Quiroga et al., 2008; Reber et al., 2017; Gelbard-Sagiv et al., 2018; Pereira et al., 2021) but also shows for the first time that they are not limited to the cortex.

Our findings that neurons in the thalamus modulate their activity according to tactile detection adds to the existing evidence in favor of the role of the thalamus for perceptual consciousness. Indeed, thalamic activity and more precisely thalamocortical loops are often considered key to gate sensory stimuli to conscious access (Ward, 2013). In non-human primates, for example, oscillatory thalamic activity predicts tactile detection (Haegens et al., 2014), and functional interactions between the somatosensory thalamus and the cortex increase when a tactile stimulus is detected (Tauste Campo et al., 2019). In humans, thalamic local field potentials and fMRI

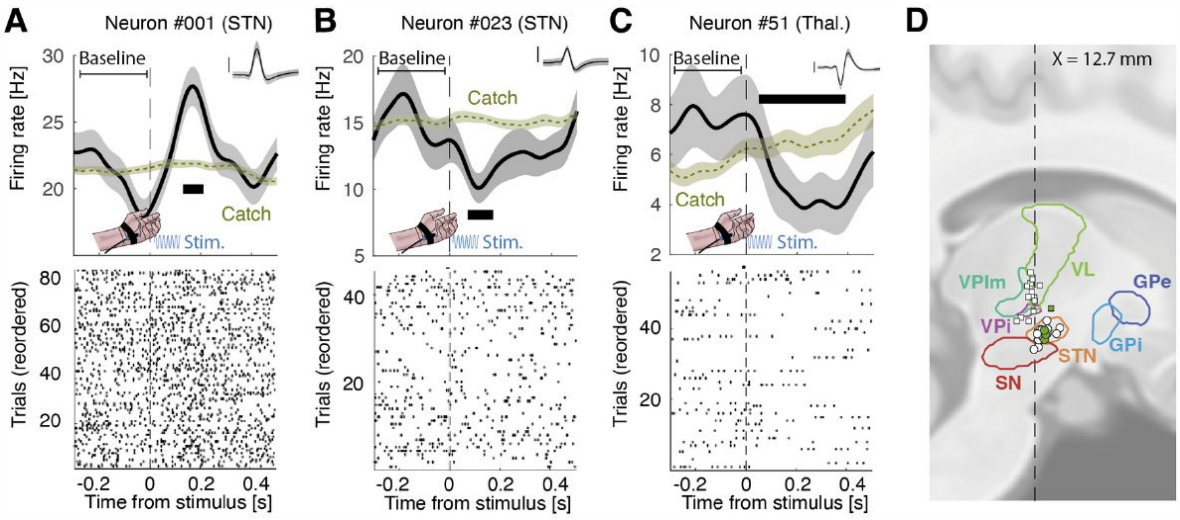
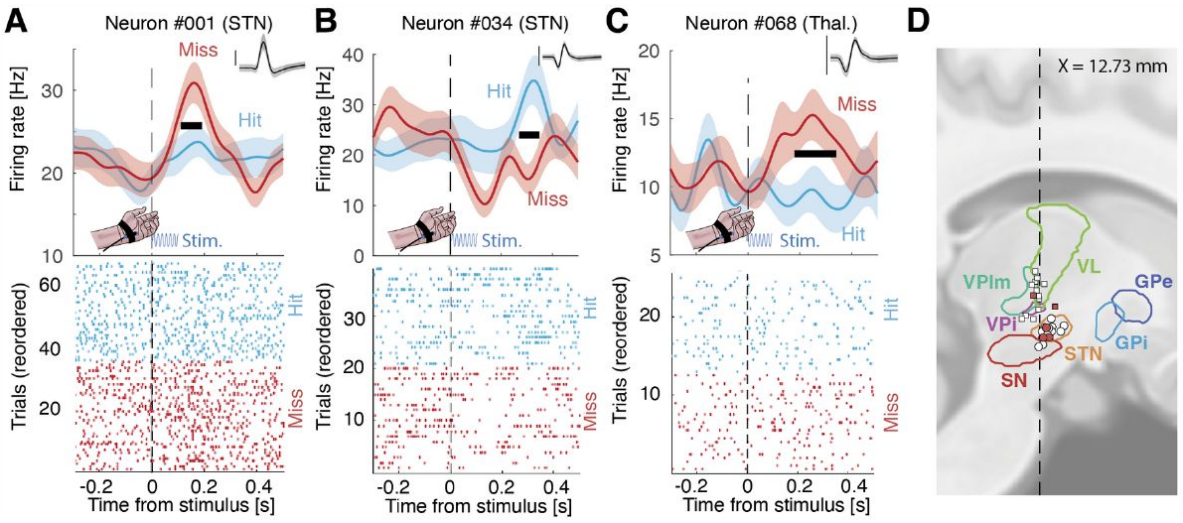



**Figure 3.**

**Representative stimulus-responsive neurons in distinct patients.**

**A-C**. Upper panels: firing rate time-locked to the onset of the stimulus (100 ms vibrotactile stimulation; blue sinusoid) for all trials. Green trace represents corresponding activity for catch trials. Thick horizontal black segments show significant time windows. Shaded areas indicate bootstrapped standard errors. Inset: corresponding action potentials (shaded area indicates standard deviation; vertical bar corresponds to 100 μV). Lower panels: raster plot. The 300 ms pre-stimulus baseline was used only for statistics. **D**. Sagittal view of recording locations for thalamic (squares) and subthalamic (circles) targets (see Figure S3B for a coronal view). Filled circles or squares are sensory-selective neurons. Legend: VL: ventral lateral thalamus, VPlm: ventral posterior lateral and medial thalamus, VPi: ventral posterior inferior thalamus, STN: subthalamic nucleus, SN: substentia nigra, GPi/e: globus pallidus internalis / externalis,




## Figure 4.

### Representative perception-selective neurons in distinct patients.

**A-C** Upper panels: firing rate time-locked to the onset of the stimulus (100 ms vibrotactile stimulation; blue sinusoid) for hits (light blue) and misses (red). Thick horizontal black segments show significant time windows. Shaded areas indicate bootstrapped standard errors. Inset: corresponding action potentials (shaded area indicates standard deviation; vertical bar corresponds to 100 μV). Lower panels: raster plot for hits (light blue) and misses (red). **D**. Sagittal view of recording locations for thalamic (squares) and subthalamic (circles) targets (see Figure S3C for a coronal view). Filled circles or squares are perception-selective neurons. Legend: VL: ventral lateral thalamus, VPlm: ventral posterior lateral and medial thalamus, VPi: ventral posterior inferior thalamus, STN: subthalamic nucleus, SN: substentia GPi/e: globus pallidus internalis / externalis,

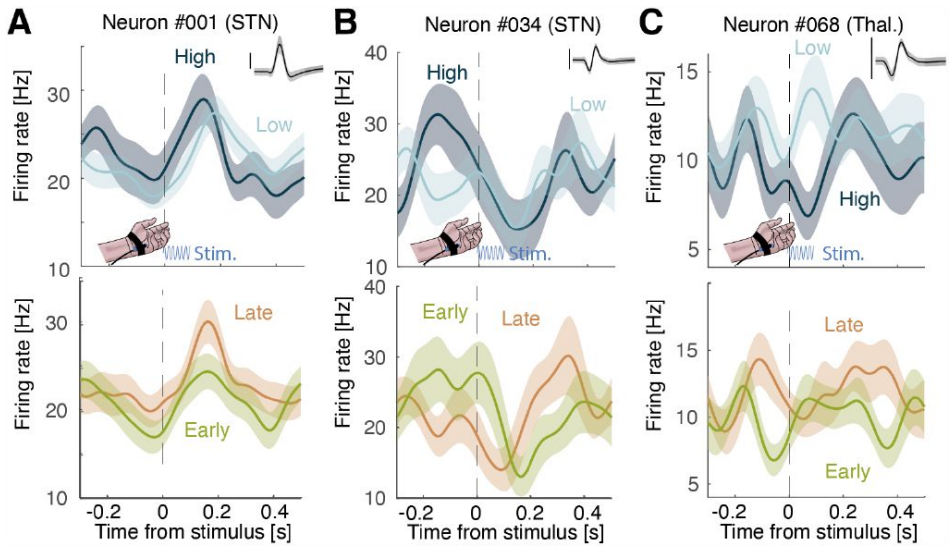



**Figure 5.**

**Neurons from Figure 4, for different stimulus intensities and onsets.**

We used the same trials as in **Figure 4** but segregated in high versus low stimulus intensities (upper panel) or short and long stimulus onsets (lower panel). We found only 5 / 32 neurons sensitive to stimulus intensity (16%; p = 0.13; permutation test) and no neurons sensitive to stimulus onset (0 / 35). None of the 5 intensity-selective neuron corresponded to a perception-sensitive neuron. **A-C**. Firing rate time-locked to the onset of the stimulus (100 ms vibrotactile stimulation; blue sinusoid) for high intensity (light blue) and low intensity (dark blue) trials (upper panel) or early (green) and late (orange) stimulus onsets. Shaded areas indicate bootstrapped standard errors. Inset: corresponding action potentials (shaded area indicates standard deviation; vertical bar corresponds to 100 μV).

activity were higher for seen vs unseen stimuli (Kronemer et al., 2022; Levinson et al., 2021) and causal effects of thalamic stimulation on the levels of consciousness have been found (Schiff et al., 2007). Future studies with higher neuronal yields will be helpful in assessing the contribution of distinct thalamic territories to tactile consciousness, focusing notably on the ventral caudal part, which contains neurons with tactile receptive fields.

Concerning the subthalamic nucleus, a possibility is that perception-selective neurons determine stimulus detection through the regulation of decisional processes. Indeed, previous studies reported a modulatory role of subthalamic activity on decisional processes, notably by elevating the decisional threshold on accumulated sensory evidence (Bogacz et al., 2007; Cavanagh et al., 2011; Green et al., 2013; Herz et al., 2016). In a recent study in which we measured the activity of cortical neurons in a similar task, we showed that evidence accumulation is also at play during conscious detection (Pereira et al., 2021). Based on this finding, we proposed that percepts fade in and out of consciousness when evidence accumulated by cortical neurons passes a given threshold (Pereira et al., 2022). The present results, therefore, indicate that the contribution of subthalamic neurons to decisional processes is not limited to discrimination tasks or motor planning, but may also regulate the threshold at which accumulated evidence gives rise to a conscious percept. Considering the inhibitory role of the subthalamic nucleus on the cortex (Mink et al., 1996), the fact that many of the perception-selective neurons we found had higher firing rate for misses than for hits suggests a role in elevating that threshold, similar to what is found in decision tasks manipulating conflict or cautiousness and requiring immediate responses (Franck et al., 2007; Cavanagh et al., 2011; Benis et al., 2016; Herz et al., 2016; Mosher et al., 2021). Thus, our results suggest that the STN plays an important role in a subcortical network gating conscious access, although it might not encode conscious content *per se* (Aru et al., 2012).

Apart from perception-selective neurons, we also found a distinct population of neurons in both the STN and thalamus that modulated their firing rate both after the cue and during the task, and therefore much before the stimulus onset. These neurons cannot be involved in detection-related processes but could instead be involved in task switching (Hikosaka & Isoda, 2010). We also found neurons that modulated their firing rates after the stimulus onset, irrespective of detection, similar to animal works in the STN (Al Tanir et al., 2023) and thalamus (Vazquez et al., 2012; Tauste Campo et al., 2018). Our results should be taken with caution as they are based on a small number of neurons due to the high complexity of intraoperative recordings, and because the number of trials we could collect was not sufficient to test the computational mechanisms underlying the neuronal activity we recorded. Future studies combining cortical and subcortical recordings would be useful to consolidate these findings and investigate how subcortical regulation interacts with the cortex. For example, the 160 ms latency we observed post-stimulus corresponds to the onset of a putative cortical correlate of consciousness, the perceptual awareness negativity (Dembski et al., 2021). We confirmed that our detection task was compatible with a contrastive analysis of consciousness in that it elicited a similar number of yes (detected stimuli or hit trials) and no responses (missed stimuli or miss trials), irrespective of stimulus intensity or stimulus onset. Nevertheless, it will be important in future studies to examine if similar subcortical responses are obtained when when stimuli are unattended (Wyart & Tallon-Baudry, 2008), task-irrelevant (Shafto & Pitts, 2015), or when participants passively experience stimuli without the instruction to report them (i.e., no-report paradigms) (Tsuchyia et al., 2015).

In sum, our study provides neurophysiological evidence from single neurons in humans that subcortical structures play a significant role in tactile detection either by themselves (Ward, 2013) or through their numerous connections with the cortex (Dehaene & Changeux, 2011). A comprehensive account of the neural correlates of consciousness should, therefore, not be cortico-centric but also consider subcortical contributions.

# Methods

## Participants

We recorded high impedance electrophysiological signals from microelectrodes inserted intraoperatively in the subthalamic nucleus of 32 participants with Parkinson disease or essential tremor undergoing deep brain stimulation electrode implantation surgeries (N = 36; 4 participants had two surgeries, one for each side). For individuals with Parkinson's disease, the age at the time of the recording was 60.4 ± 2.7 years and the average UPDRS III score was 40.6 ± 3.0 prior to surgery and was reduced to 20.8 ± 2.8 after the surgery ($p = 0.0015$, $z = 3.18$). We also recorded intraoperatively in the thalamus of individuals with essential tremor undergoing deep brain stimulation surgeries. The age at the time of the recording was 68.9 ± 3.2 years and the average TETRA motor score was 20.1 ± 2.9 prior to surgery. The study was approved by the institutional review board of the West Virginia University Hospital (WVU02HSC17; #1709745061) and all participants provided written informed consent prior to any data collection.

## Experimental procedure

Participants performed a tactile detection task programmed in Matlab using the Psychophysics toolbox (Brainard, 1997; Pelli, 1997; Kleiner et al., 2007). When possible, participants were trained a few days before the surgery (N = 18 / 36 surgeries). Participants sat in a reclining chair in a quiet room (training session) or were lying in the operating room (main session). Every trial started with a 300 ms long auditory "go" cue delivered through an external loudspeaker placed near the participants. Following the end of the go cue and a delay of 500 ms, a 100 ms vibrotactile stimulus could be delivered at any time during a two second stimulation window (i.e., uniform distribution between 0.8 and 2.8 s after the onset of the go cue; **Figure 1A**) on the lateral palm contralateral to the deep brain implant. Stimuli were applied using a MMC3 Haptuator vibrotactile device from TactileLabs Inc. (Montréal, Canada) driven by a 230 Hz sinusoid audio signal. Participants reported orally whether they felt the stimulus or not and whether they were confident in their answer or not after an auditory "respond" cue played one second after the end of the stimulation window. The participants responses could thus consist in "yes, sure", "yes, unsure", "no, sure" and "no, unsure". The task was stopped after two sessions of 71 trials, or before in case of discomfort or other clinical constraints. As –upon waking from anesthesia– most participants did not use both confidence levels, confidence data was therefore not analyzed.

To keep the vibrotactile stimulus intensity around the detection threshold, we first conducted a rough threshold search by presenting a series of stimuli whose intensity decreased by steps of 5% until participants reported not feeling them anymore. Then we presented series of low intensity stimuli whose intensities increased by step of 5% until participants reported feeling them again. These procedures were repeated until the experimenter deemed the results satisfying. We took the average between the thresholds obtained during these procedures as a seed for the main task. During the main task, a 1up/1down adaptive staircase procedure (Levitt, 1971) ensured that the intensity was kept around the perceptual threshold by increasing the intensity by 5% after miss trial and decreasing the intensity by 5% after a hit trial. Of note, the absolute stimulus intensity is not informative and cannot be compared across patients and sessions, as it varied according to different factors (e.g. the length of the cable or the manner with which the tactile stimulator was strapped onto the palm).

## Surgical procedure

STN or thalamus targets and trajectories were defined preoperatively using CranialSuite (Neurotargeting Inc., Nashville, US) based on MRI scans. Both targets were then defined with respect to the AC-PC (commissural) line using standard atlas-based methods and refined based on

individual anatomy. The entry point was chosen approximately 2 to 3 cm from the midline and 1 cm anterior from the coronal suture and adjusted to individual anatomy in order to avoid traversing brain sulci, lateral ventricles or the medial bridging veins. Scalp incisions and burr-hole drilling were performed under local (lidocaine) and general (propofol) anesthesia and a microelectrode (FHC, Maine, US) was inserted through a guide cannula using a microdrive placed either on a Leksell frame (N = 13 surgeries) or a 3D printed mould (N = 23 surgeries).

## Electrophysiology

Once the microelectrode reached the target brain structure (STN or thalamus), the speed of the microdrive was reduced and neuronal activity was streamed to a loudspeaker, allowing the electrophysiologist to verify the depth of the preplanned trajectory. The main research task was initiated when a neuron showed stable activity for a few tens of seconds and the anatomical localization was confirmed by the electrophysiologist. Recording depths were saved and used offline to define the anatomical localization (see Anatomical localization section). Electrophysiological data were recorded from the 5 mm tip of the microelectrode, referenced to the guide cannula and an adaptive line noise canceller was applied. Data were digitized either using a Guideline 4000 LP+ amplifier (FHC, Maine, US) at 30 kHz (N = 21 surgeries), or using a Guideline 5 amplifier (FHC, Maine, US) at 32 kHz and resampled offline to 30 kHz (N = 14 surgeries).

## Anatomical localization

For 34 / 50 neurons, preoperative MRI and postoperative CT scans (co-registered in patient native space using CranialSuite) were available to precisely reconstruct surgical trajectories and recording locations (for the remaining 16 neurons, localizations were based on neurosurgical planning and confirmed by electrophysiological recordings at various depths). Recording depths were inspected along the trajectories in patient native space, projected to an MNI-coordinate space and compared against the Ilinsky atlas (Ilinsky et al., 2018) which delineates distinct thalamic sub-territories based on a marker of ψ-aminobutyric acid on sections post-mortem human brains.

## Behavioral analyses

We used R 4.1.2 (Team R, 2020) and the tidyverse (Wickham et al., 2019) package to analyze behavioral data. Permutation tests were performed by permuting hit and miss trials over 1000 iterations for each participant. Non-parametric p-values were estimated by counting the permutations for which the difference between hits and misses was higher in the observed compared to the shuffled data.

As titrating and keeping the vibrotactile stimulation intensity to the perceptual level after anesthesia was a challenging task, we took great care in keeping only the highest quality recordings. We estimated the trial-by-trial hit-rate using a sliding window of 11 trials (for the first and last 5 trials, we mirrored trials to avoid border effects). Any trial with a hit-rate out of the ]25, 75[ % range were removed from further analysis comparing hit to miss trials. If less than 10 hit and 10 miss trials were kept by this procedure, the session (and its corresponding neurons) was removed from subsequent analyses (13 / 48 sessions; 27 %).

## Spike sorting and firing rate estimation

Each microelectrode recording was filtered between 300 and 3000 Hz and visually inspected. Artifacts such as cross-talk from the participants' vocal responses were marked and replaced by noise with a standard deviation matching the second pre- and post-artifact. We performed this procedure to avoid spuriously lowering the thresholds for neuronal spike detection. The timing of these artifactual epochs were saved in order to reject affected trials in later analyses. Neuronal spikes were detected and clustered using an online semi-automatic spike sorting algorithm (OSort) (Rutishauser et al., 2006). Each resulting cluster of neurons was inspected based on common

metrics such as spike waveform, percentage of inter-spike interval below 3 ms, signal-to-noise ratio and power spectral densities and possibly merged with other clusters. Finally, the resulting curated neurons were labeled as *putative single neuron* or *multiunit*, depending on the spike waveforms, peak amplitude distribution and the percentage of inter-spike interval below 3 ms. Electrophysiological signals were realigned either to the onset of the "go" cue (**Figures 2**) or to the onset of the stimulus (**Figures 3**-**4**), which was precisely obtained by applying a matched filter to a copy of the audio signal used to drive the vibrotactile stimulator we simultaneously recorded with the electrophysiological data. We estimated instantaneous firing rates using a sliding Gaussian kernel with a standard deviation of 40 ms and 1 ms steps. When displaying the resulting average firing rates over time, we estimated the standard error of the mean using a bootstrap procedure with 1000 resamplings.

## Identification of selective neurons

To thoroughly control for false positives and possibly non-normal distributions, we exclusively used non-parametric statistics (Wilcoxon rank sum test, sign test), coupled with permutation tests. For each analysis, we verified that the reported number of neurons could not have been obtained by chance by comparing this number to a null distribution using permutation tests (Maris & Oostenveld, 2007). For paired tests with respect to a baseline, we randomly flipped the sign of the difference between the firing rate during the trial and during the baseline and for unpaired tests, we randomly shuffled the conditions (i.e. a hit trial could be randomly assigned to a hit or a miss trial). To obtain a p-value, we compared the number of selective neurons to a null distribution obtained by randomly permuting the data 1000 times. This procedure allowed us to show that the number of selective neurons could not have been obtained by chance while controlling for multiple comparisons over time. Similarly, to test whether the proportion of neurons was different in the STN compared to the thalamus, we compared the absolute difference in the proportion of neurons in each anatomical location to a null distribution obtained by random permutations.

To identify cue-selective neurons we compared the number of spikes in a 500 ms baseline preceding the "go" cue to the number of spikes in a 500 ms period following the offset of the "go cue" using a two-tailed non-parametric sign test. Similarly, we identified task-responsive neurons by comparing the mean number of spikes in a 500 ms baseline preceding the "go" cue to the mean number of spikes during the 2 s stimulation window and performing a permutation test. We compared the differences in the proportion of selective neurons in the STN and thalamus, to the same differences observed in the shuffled data to assess its significance. Finally, we also compared the number of cue- and task-selective neurons to the same number observed in the shuffled data to assess whether the overlap was significant.

To identify detection-selective neurons, we looked for differences in the firing rates during the first 400 ms post-stimulus onset, assuming that subcortical signatures of stimulus detection ought to be found early following its onset. To correct for possible drifts occurring during the trial, we subtracted the cue-locked activity from catch trials to the cue-locked activity of stimulus-present trials before realigning to stimulus onset. We defined a cluster as a set of adjacent time points for which the firing rates were significantly different between hits and misses, as assessed by a non-parametric Wilcoxon rank sum test. A putative neuron was considered perception-selective when the length of a cluster was above 80 ms, corresponding to twice the standard deviation of the smoothing kernel used to compute the firing rate. Whether for the shuffled data or the observed data, if more than one cluster was obtained, we discarded all but the longest cluster. This permutation test allowed us to control for multiple comparisons across time and participants.

## Data and code availability

Data and code necessary to replicate our results are available online (*https://gitlab.com/michael.pereira/subcortical-ncc*).

Further information and requests should be directed to and will be fulfilled by the lead contact, Michael Pereira (michael.pereira@univ-grenoble-alpes.fr).

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**Reviewer #1 (Public Review):**

Summary:

A cortico-centric view is dominant in the study of the neural mechanisms of consciousness. This investigation represents the growing interest in understanding how subcortical regions are involved in conscious perception. To achieve this, the authors engaged in an ambitious and rare procedure in humans of directly recording from neurons in the subthalamic nucleus and thalamus. While participants were in surgery for the placement of deep brain stimulation devices for the treatment of essential tremor and Parkinson's disease, they were awakened and completed a perceptual-threshold tactile detection task. The authors identified individual neurons and analyzed single-unit activity corresponding with the task phases and tactile detection/perception. Among the neurons that were perception-responsive, the authors report changes in firing rate beginning ~150 milliseconds from the onset of the tactile stimulation. Curiously, the majority of the perception-responsive neurons had a higher firing rate for missed/not perceived trials. In summary, this investigation is a valuable addition to the growing literature on the role of subcortical regions in conscious perception.

Strengths:

The authors achieved the challenging task of recording human single-unit activity while participants performed a tactile perception task. The methods and statistics are clearly explained and rigorous, particularly for managing false positives and non-normal distributions. The results offer new detail at the level of individual neurons in the emerging recognition of the role of subcortical regions in conscious perception.

Weaknesses:

"Nonetheless, it remains unknown how the firing rate of subcortical neurons changes when a stimulus is consciously perceived." (lines 76-77) The authors could be more specific about what exactly single-unit recordings offer for interrogating the role of subcortical regions in conscious perception that is unique from alternative neural activity recordings (e.g., local field potential) or recordings that are used as proxies of neural activity (e.g., fMRI).

Related comment for the following excerpts:

"After a random delay ranging from 0.5 to 1 s, a "respond" cue was played, prompting participants to verbally report whether they felt a vibration or not. Therefore, none of the reported analyses are confounded by motor responses." (lines 97-99).

"These results show that subthalamic and thalamic neurons are modulated by stimulus onset, irrespective of whether it was reported or not, even though no immediate motor response was required." (lines 188-190).

"By imposing a delay between the end of the tactile stimulation window and the subjective report, we ensured that neuronal responses reflected stimulus detection and not mere motor responses." (lines 245-247).

It is a valuable feature of the paradigm that the reporting period was initiated hundreds of milliseconds after the stimulus presentation so that the neural responses should not represent "mere motor responses". However, verbal report of having perceived or not perceived a stimulus is a motor response and because the participants anticipate having to make these reports before the onset of the response period, there may be motor preparatory

activity from the time of the perceived stimulus that is absent for the not perceived stimulus. The authors show sensitivity to this issue by identifying task-selective neurons and their discussion of the results that refer to the confound of post-perceptual processing. Still, direct treatment of this possible confound would help the rigor of the interpretation of the results.

"When analyzing tactile perception, we ensured that our results were not contaminated with spurious behavior (e.g. fluctuation of attention and arousal due to the surgical procedure)." (lines 118-117).

Confidence in the results would be improved if the authors clarified exactly what behaviors were considered as contaminating the results (e.g., eye closure, saccades, and bodily movements) and how they were determined.

The authors' discussion of the thalamic neurons could be more precise. The authors show that only certain areas of the thalamus were recorded (in or near the ventral lateral nucleus, according to Figure S3C). The ventral lateral nucleus has a unique relationship to tactile and motor systems, so do the authors hypothesize these same perception-selective neurons would be active in the same way for visual, auditory, olfactory, and taste perception? Moreover, the authors minimally interpret the location of the task, sensory, and perception-responsive neurons. Figure S3 suggests these neurons are overlapping. Did the authors expect this overlap and what does it mean for the functional organization of the ventral lateral nucleus and subthalamic nucleus in conscious perception?

"We note that, 6 out of 8 neurons had higher firing rates for missed trials than hit trials, although this proportion was not significant (binomial test: $p = 0.145$)." (lines 215-216).

It appears that in the three example neurons shown in Figure 4, 2 out of 3 (#001 and #068) show a change in firing rate predominantly for the missed stimulations. Meanwhile, #034 shows a clear hit response (although there is an early missed response - decreased firing rate - around 150 ms that is not statistically significant). This is a counterintuitive finding when compared to previous results from the thalamus (e.g., local field potentials and fMRI) that show the opposite response profile (i.e., missed/not perceived trials display no change or reduced response relative to hit/perceived trials). The discussion of the results should address this, including if these seemingly competing findings can be rectified.

The authors report 8 perception-responsive neurons, but there are only 5 recording sites highlighted (i.e., filled-in squares and circles) in Figures S3C and 4D. Was this an omission or were three neurons removed from the perception-responsive analysis?

Could the authors speak to the timing of the responses reported in Figure 4? The statistically significant intervals suggested both early (~160-200ms) to late responses (~300ms). Some have hypothesized that subcortical regions are early - ahead of cortical activation that may be linked with conscious perception. Do these results say anything about this temporal model for when subcortical regions are active in conscious perception?

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**Reviewer #2 (Public Review):**

The authors have studied subpopulations of individual neurons recorded in the thalamus and subthalamic nucleus (STN) of awake humans performing a simple cognitive task. They have carefully designed their task structure to eliminate motor components that could confound their analyses in these subcortical structures, given that the data was recorded in patients with Parkinson's Disease (PD) and diagnosed with an Essential Tremor (ET). The recorded data represents a promising addition to the field. The analyses that the authors have applied can serve as a strong starting point for exploring the kinds of complex signals

that can emerge within a single neuron's activity. Pereira et. al conclude that their results from single neurons indicate that task-related activity occurs, purportedly separate from previously identified sensory signals. These conclusions are a promising and novel perspective for how the field thinks about the emergence of decisions and sensory perception across the entire brain as a unit.

Despite the strength of the data that was obtained and the relevant nature of the conclusions that were drawn, there are certain limitations that must be taken into consideration:

(1) The authors make several claims that their findings are direct representations of consciousness identifiable in subcortical structures. The current context for consciousness does not sufficiently define how the consciousness is related to the perceptual task.

(2) The current work would benefit greatly from a description and clarification of what all the neurons that have been recorded are doing. The authors' criteria for selecting subpopulations with task-relevant activity are appropriate, but understanding the heterogeneity in a population of single neurons is important for broader considerations that are being studied within the field.

(3) The authors have omitted a proper set of controls for comparison against the active trials, for example, where a response was not necessary. Please explain why this choice was made and what implications are necessary to consider.

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**Reviewer #3 (Public Review):**

Summary:

This important study relies on a rare dataset: intracranial recordings within the thalamus and the subthalamic nucleus in awake humans, while they were performing a tactile detection task. This procedure allowed the authors to identify a small but significant proportion of individual neurons, in both structures, whose activity correlated with the task (e.g. their firing rate changed following the audio cue signalling the start of a trial) and/or with the stimulus presentation (change in firing rate around 200 ms following tactile stimulation) and/or with participant's reported subjective perception of the stimulus (difference between hits and misses around 200 ms following tactile stimulation). Whereas most studies interested in the neural underpinnings of conscious perception focus on cortical areas, these results suggest that subcortical structures might also play a role in conscious perception, notably tactile detection.

Strengths:

There are two strongly valuable aspects in this study that make the evidence convincing and even compelling. First, these types of data are exceptional, the authors could have access to subcortical recordings in awake and behaving humans during surgery. Additionally, the methods are solid. The behavioral study meets the best standards of the domain, with a careful calibration of the stimulation levels (staircase) to maintain them around the detection threshold, and an additional selection of time intervals where the behavior was stable. The authors also checked that stimulus intensity was the same on average for hits and misses within these selected periods, which warrants that the effects of detection that are observed here are not confounded by stimulus intensity. The neural data analysis is also very sound and well-conducted. The statistical approach complies with current best practices, although I found that, in some instances, it was not entirely clear which type of permutations had been performed, and I would advocate for more clarity in these instances. Globally the figures are

nice, clear, and well presented. I appreciated the fact that the precise anatomical location of the neurons was directly shown in each figure.

Weaknesses:

Some clarification is needed for interpreting Figure 3, top rows: in my understanding the black curve is already the result of a subtraction between stimulus present trials and catch trials, to remove potential drifts; if so, it does not make sense to compare it with the firing rate recorded for catch trials.

I also think that the article could benefit from a more thorough presentation of the data and that this could help refine the interpretation which seems to be a bit incomplete in the current version. There are 8 stimulus-responsive neurons and 8 perception-selective neurons, with only one showing both effects, resulting in a total of 15 individual neurons being in either category or 13 neurons if we exclude those in which the behavior is not good enough for the hit versus miss analysis (Figure S4A). In my opinion, it should be feasible to show the data for all of them (either in a main figure, or at least in supplementary), but in the present version, we get to see the data for only 3 neurons for each analysis. This very small selection includes the only neuron that shows both effects (neuron #001; which is also cue selective), but this is not highlighted in the text. It would be interesting to see both the stimulus-response data and the hit versus miss data for all 13 neurons as it could help develop the interpretation of exactly how these neurons might be involved in stimulus processing and conscious perception. This should give rise to distinct interpretations for the three possible categories. Neurons that are stimulus-responsive but not perception-selective should show the same response for both hits and misses and hence carry out indifferently conscious and unconscious responses. The fact that some neurons show the opposite pattern is particularly intriguing and might give rise to a very specific interpretation: if the neuron really doesn't tend to respond to the stimulus when hits and misses are put together, it might be a neuron that does not directly respond to the stimulus, but whose spontaneous fluctuations across trials affect how the stimulus is perceived when they occur in a specific time window after the stimulus. Finally, neuron #001 responds with what looks like a real burst of evoked activity to stimulation and also shows a difference between hits and misses, but intriguingly, the response is strongest for misses. In the discussion, the interesting interpretation in terms of a specific gating of information by subcortical structures seems to apply well to this last example, but not necessarily to the other categories.

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