The role of secondary motor cortex in multisensory decision making

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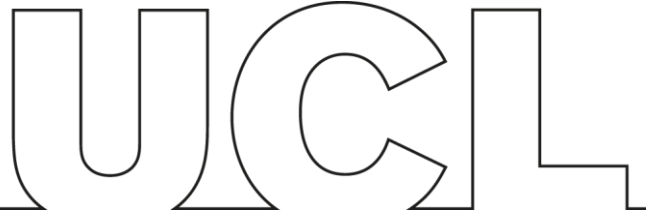
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Abstract

Combining sensory information from various modalities for perceptual decision-making offers several advantages and is essential for the survival of both humans and animals. Not much is known about which brain regions are involved in spatial localization using audiovisual integration. Previous work in our lab has isolated the secondary motor cortex (M2) as being involved. I explore this further by training mice in a task requiring audiovisual integration. I then record from the M2 using high-density electrophysiology. Analyzing this data, I found neurons responsive to multimodal as well as unimodal auditory and visual stimuli. The neurons are generally more responsive to auditory, rather than visual, stimuli. There was low correlation between the auditory and visual responses. There were also neurons that were sensitive to the task mode, whether active or passive, with more neurons being responsive in the active mode. A relatively large percentage of neurons (10-11%) differed significantly in their response to left and right sided auditory stimuli, but only in 1 of the 3 mice I recorded from. These findings suggest a role for M2 in multisensory decision making and should enable further research in this field.

Introduction

The ability to integrate information from different sources is an ethologically important process and it offers animals tremendous advantages. Spatial localization using multimodal stimuli, for example, is critical for both predator and prey in the wild and for pedestrians crossing the street. Studies have shown that integrating information from several modalities is advantageous for perceptual decision making (Murray and Wallace, 2011). In addition, multisensory integration enhances speed and accuracy of responses (Calvert and Thesen, 2004; Stevenson *et al.*, 2014). Accumulating evidence also shows that deficits in multisensory processing are present in psychological disorders, including children with autism (Foss-Feig *et al.*, 2010). However, the mechanism by which the brain integrates multimodal stimuli is not yet clearly defined.

There have been several conflicting studies regarding the putative site of spatial integration, particularly with respect to audiovisual localization. In earlier studies, several brain regions such as the superior colliculus, association cortex, and the dorsal medial superior temporal area have been proposed as sites of multisensory integration (Angelaki, Gu and DeAngelis, 2009). Studies in rats have reported a role for the posterior parietal cortex (PPC) in spatial integration but inactivating the PPC did not impair behavior (Raposo, Kaufman and Churchland, 2014). The major drawback of these model organisms is that high-throughput methods are not available for them. On the other hand, the precise advantage that mice offer is that we can head-fix them and that we have a larger variety of genetic (e.g. optogenetics), psychophysical and optical imaging tools available to us. Resources such as the Allen Brain Atlas and the Mouse Brain Architecture Project make mice a particularly viable model for studying sensory processing and decision making

(Carandini and Churchland, 2013). However, very few studies have examined multisensory integration in mice. One such study, by Song *et al.* (2017), reported an auditory dominance over visual stimuli during cross-modal activation due to feedforward inhibition of the visual cortical inputs to the PPC by the auditory cortical inputs.

Taking an unbiased approach in our lab, optogenetics was used to inactivate 52 different regions of the mouse dorsal brain. Contrary to previous studies (Angelaki, Gu and DeAngelis, 2009; Raposo, Kaufman and Churchland, 2014; Song *et al.*, 2017), we found no evidence for a multisensory role of PPC. Instead, we identified the secondary motor (M2) region of frontal cortex as being critically involved in multisensory integration as inactivating M2 impaired behavior. This project builds on the work done so far in our lab by recording from the M2 while the mice are engaged in a task requiring audio-visual integration. We used neuropixels probes, which were jointly developed in the lab, to record from the mice (Jun *et al.*, 2017). These probes offer tremendous advantages over traditional electrophysiological recording methods as the large volume coverage offered by the probes allows us to record from hundreds of sites per probe simultaneously. Additionally, the probes have a small cross-sectional area which minimizes brain tissue damage. The dense recording sites and high channel counts give the probes a high spatiotemporal resolution, yielding well isolated neuronal spiking activity (Jun *et al.*, 2017). The goal of my project was to find out how the secondary motor cortex neurons encode this integration. To do so, I trained mice to perform the task. Following the training, I recorded from the M2 using neuropixels probes. I then analyzed the behavior and spiking data on MATLAB which allowed us to build a more complete picture of the neural correlates of audiovisual integration in M2.

Methods

Surgery and training: To understand the role of M2, I first trained mice in a task requiring audiovisual integration. All the mice used were female. I used 5 mice for the actual recording which required training 6 mice in a modified version of the 2-alternative forced-choice task described by Burgess *et al.* (2017). Prior to training, the mice underwent surgery. Isoflurane (Merial; 3.5% for induction and 1-2% during surgery) and lidocaine (local; 6mg/kg, Hameln pharmaceuticals ltd) were used for anesthesia. Carprofen (5 mg/kg; Rimadyl, Pfizer) was administered intraoperatively via the subcutaneous route for systemic analgesia. Eyes were covered with chloramphenicol (Martindale Pharmaceuticals Ltd). The animal was placed into a stereotaxic apparatus and the skin and connective tissue surrounding the area of interest were removed. A custom-made head-plate was positioned above the area of interest and attached to the bone with Superbond C&B (Sun Medical). Throughout all surgical procedures, the body temperature was stabilized at 37°C by heating pads. Subcutaneous injections of 0.01 ml/g/h of Hartmann's solution were given. After the surgery, the animal was placed into a heated cage for recovery from anesthesia. Mice were given three days to recover while being treated with carprofen. The surgeries were performed by Ms. Charu Reddy and Dr. Philip Coen.

The mice were water restricted to encourage adaptation to the training rig and increase motivation for water reward. Mice were mostly trained for 5 days a week. Both the training and experimental rigs had three screens and seven speakers. On each trial, the mice were head-fixed and were presented with either a visual or an auditory stimulus (unimodal) or both simultaneously (cross-modal). The stimuli could be either from the same (coherent trials) or opposite (conflict trials)

directions. The mice were required to turn the wheel in order to center the stimuli. The visual stimulus was a gabor with different contrasts (10% to 80%). The auditory stimulus was filtered pink noise at 8-16 kHz. The stimuli were flickering at 8 Hz. There was an inter-trial interval of 1-2 seconds. The performance of the mice on the task has been well established by previous work done in our lab. The task was well suited for this purpose as it is closed-loop, allowing rapid learning; and is compatible with neuropixels recordings. The behavioral performance was examined using classic psychophysical analyses, including psychometric curves.

Recordings: Once the mice were able to perform the task to a reasonable criterion, which typically took around 4-6 weeks of training, they were shifted to the experimental rig. After an adaptation period of about 10 days, recordings were performed from the M2. On the day of the recordings, mice were briefly anesthetized with isoflurane while two craniotomies were made above the areas of interest (M2), 2 mm anterior and 1.5 mm lateral to the bregma., either with a dental drill or a biopsy punch. After at least three hours of recovery, mice were head-fixed in the setup. Probes had a soldered connection to short external reference to ground; the ground connection at the headstage was subsequently connected to an Ag/AgCl wire positioned on the skull. The craniotomies, as well as the wire, were covered with a saline bath. Probes were advanced through the saline and through the dura at a 45° angle to the horizontal., then lowered to their final position at ~10µm/sec. Electrodes were allowed to settle for ~5 min before starting recording. Recordings were made in external reference mode with LFP gain = 250 and AP gain = 500. We recorded both during the task and during the passive presentation of stimuli, to see if neural responses are different in M2 while the animal is engaged in the task. The passive mode had the same stimulus presentations as the active mode of the task, but the water reward was switched off.

These craniotomies allowed us 5-7 days of recordings from the site, before the growth of bony and scar tissue obstructed the site completely. We then performed a second set of craniotomies near the first ones, to record for a further 5-7 days. Following this second set of recordings, the mice were culled.

Data analysis: Processing the behavioral and electrophysiological data involved manually sorting the good spikes from bad ones, using Kilosort (Pachitariu *et al.*, 2016). The automated processing already labelled the clusters (spikes from a single neuron) which it thought to be noise. The manual stage involved checking these decisions and classifying the other clusters into noise, multi-unit activity (MUA) or good spikes. The decision process involved 3 stages – checking the amplitude (low amplitude not good), the shape of the waveform (noise-like?) and the presence of refractory period on the correlogram (MUA/noise had no or very small refractory periods). Generally, clusters meeting at least 2 of the 3 criteria were labelled good. Only these good spikes were used for my study. These were processed further, and the resulting data was used for analysis using MATLAB. Overall, 8166 neurons were included in the passive data and 8043 were included in the active data (neuron clusters which do not spike at all were excluded automatically by the processing software). Not all these clusters were from the M2.

As a first step in analysis, I looked at the fraction of neurons responding to auditory and visual stimuli respectively. This analysis was done in passive recordings as the active mode of the task had on onset tone from the middle speaker in all trials, which would made it difficult to differentiate the effect of visual stimuli. To compare the change in firing rate in response to auditory stimuli, a time window of 100-500 milliseconds before stimulus onset and 50-100 ms after the stimulus onset was used. For visual stimuli, the window after the stimulus onset

was changed to 100-150 ms, as visual responses were observed to be slower as compared to auditory responses. A paired t-test was used to detect the changes in response for every trial, with a significance level of $p < 0.01$.
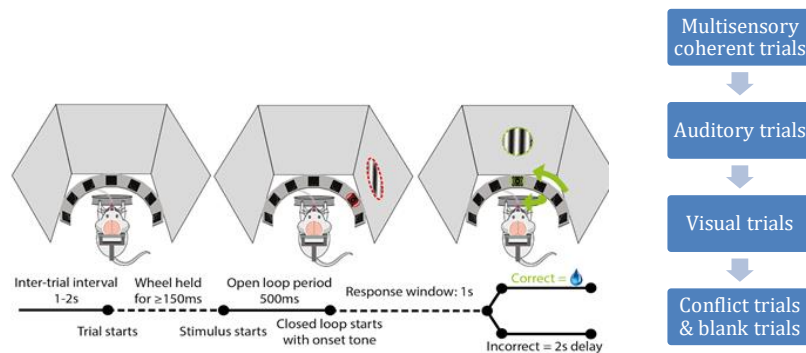
I then looked for any correlation between auditory and visual responsive neurons. This analysis was also done in passive mode with the same time windows as above. Only the neurons which were marked as responsive to either auditory or visual stimuli, from the above analysis, were included here. A best-fit line was plotted and R^2 and p values were calculated.

Finally, I looked at whether there were neurons whose responses differed significantly when the stimuli were presented from either the left or the right. This analysis was done for both active and passive recordings. Again, only the neurons responding to either auditory or visual stimuli were included. For the active mode, trials in which the mouse did not respond (timed out) were excluded. An unpaired t-test was used, with a significance level of $p < 0.01$.
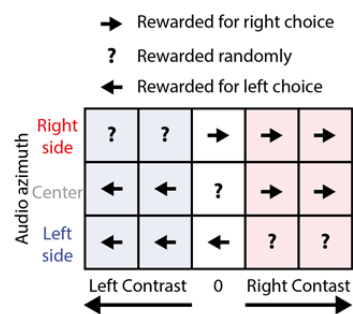
Results

I trained the mice in a 2-alternative forced choice (2-AFC) task, in which they moved a wheel in order to center the auditory and/or visual stimuli. The total training period for each subject was around 4-6 weeks. This time has been found in our lab to be optimal as the animals are well trained and it avoids the pitfalls of a shorter training period. These include highly variable behavioral performance, which makes it difficult to extract any relevant information from the data. Also, well trained animals have little confusion about the task structure, and most of the errors they make stem from confusion in their perception of the stimulus. This makes the behavioral performance easier to analyze, leading to the well-defined psychometric curves as described below (Fig. 1 (d)).
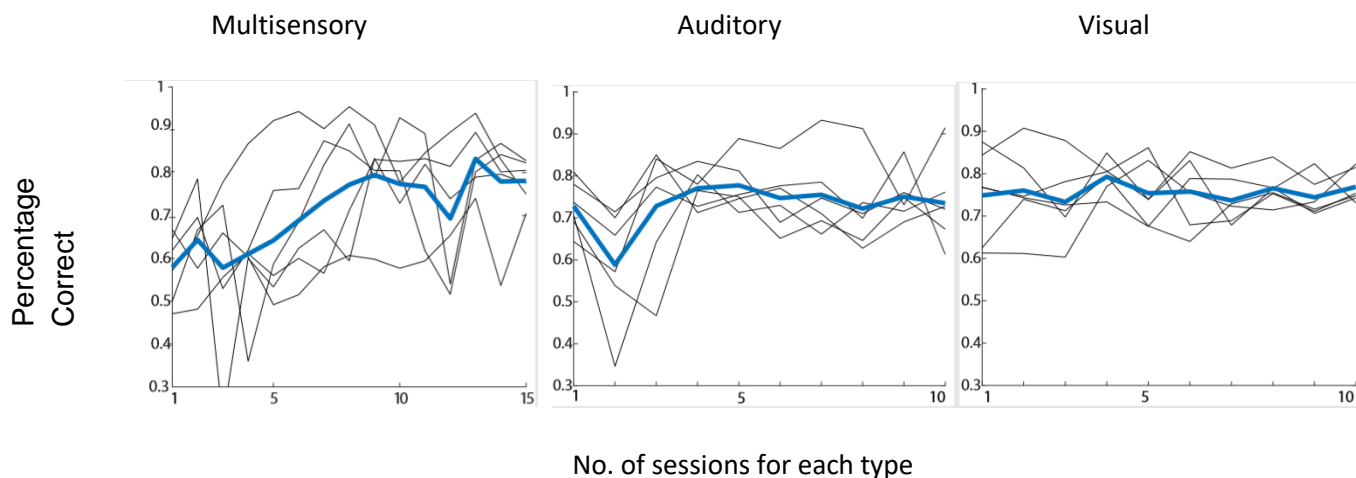
Fig. 1 (c) shows the learning rates of all the mice at the various stages of training. I began training the mice with multisensory stimuli from the same direction i.e. coherent (no conflict) trials. When the mice performed well, unisensory auditory and visual stimuli were introduced successively. These were later followed by blank trials and conflict trials, for which there was no correct response. The mice learn quickly and generalize to visual and auditory trials. Out of the 6 mice I trained, I failed to learn the task to a satisfactory standard and was removed from the study. Fig. 1 (d) shows the fraction of rightward choices made by the mice in various trial conditions. The three lines showing the performance in the auditory left, right and center are clearly separated showing that mice combine the information from the auditory and visual stimuli while making decisions. The grey line, showing the auditory amplitude in the middle, is centered at the origin, indicating minimal bias.
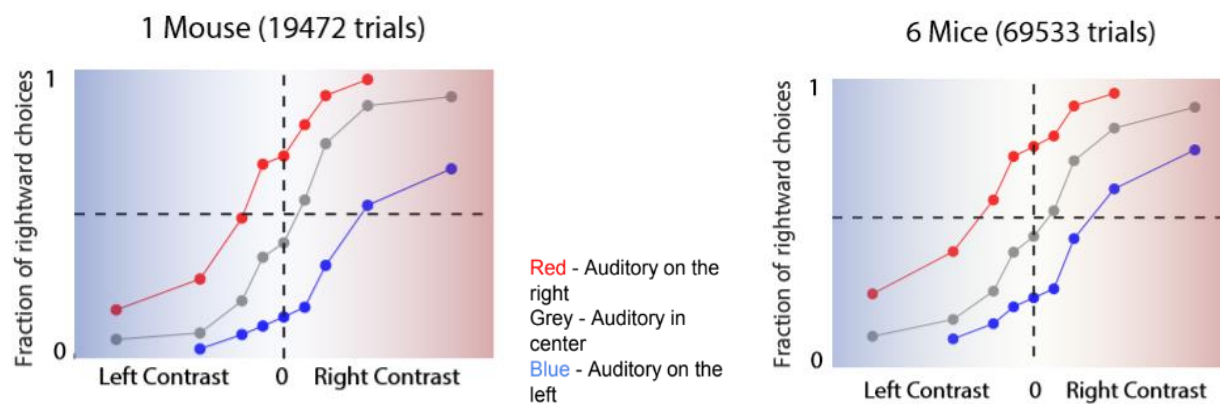
(a) Experimental set up & timeline

(b) Reward structure

Multisensory
coherent trials

Auditory trials

Visual trials

Conflict trials
& blank trials

Multisensory   Auditory   Visual

Percentage
Correct

No. of sessions for each type

(c) Learning rate

1 Mouse (19472 trials)

6 Mice (69533 trials)

Red - Auditory on the right
Grey - Auditory in center
Blue - Auditory on the left

(d) Training performance

Fig 1. Training mice in the task (a) The experimental set-up and the timeline for the task. **(b)** The reward structure: the X-axis is the visual contrast in either direction and the Y-axis is the auditory stimuli. The mice get rewarded for correctly centering the unidirectional stimuli. For bidirectional/conflict stimuli as well as blank trials (which have an onset sound from the middle speaker) the mice get rewarded randomly. At the end of the training period, all mice were able to perform the task to a reasonable criterion ($\geq$ 75% correct responses). **(c)** The training performance of the mice at various stages of learning: we started with multisensory coherent trials, followed by auditory and then visual trials. The grey lines represent the individual mice, while the blue line is the average performance of all mice for each trial type. **(d)** The training performance of the mice expressed as fraction of rightward choices: the blue background represents increasing visual contrast for visual stimuli on the left, while the red background represents the same on the right. Blue lines on red background, and vice-versa, represent conflict trials, while lines on the same colored background are coherent trials. The example mouse performed 19472 trials, while overall, the mice performed 69533 trials.

The visual stimuli in our task had varying contrasts, from 10% to 80%. The auditory stimuli also varied in the direction of presentation. This allowed us to differentiate the effects of any bias or guessing by the subjects while performing the behavior. As a result, we obtained psychometric curves which spanned most of the Y-axis, showing good training and high engagement of the subjects. The grey line was also centered at the origin, showing a minimal bias. These are indicative of a well-performed psychophysical experiment (Carandini and Churchland, 2013).

We used neuropixels probes to record from ~8000 neurons from 3 mice (we had to cull two trained mice early as they developed ocular infections). Inserting two electrodes at a time yielded simultaneous recordings from hundreds of neurons in each recording session. In total we performed 43 insertions in the 3 mice. We identified the firing times of individual neurons using Kilosort (Pachitariu *et al.*, 2016) and determined their anatomical locations by combining electrophysiological features with the histological reconstruction of fluorescently

labeled probe tracks. Fig. 2 (b) shows a section of the mouse brain with the probe tract marked using a fluorescent dye. The histology was performed by Dr. Laura Funnell. The picture is overlaid with a diagram from the Allen Mouse Brain Atlas with the primary and secondary motor cortices highlighted in blue. This confirms that the probes did record from the M2. Fig. 2 (c) shows example neurons sensitive to multimodal stimuli, auditory stimuli only and to task mode respectively. The movement markers show that the neuron indeed responds to the presentation of the stimulus, rather than movement.
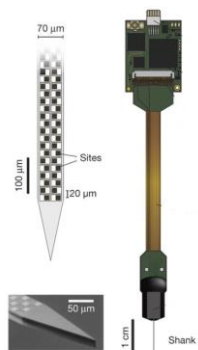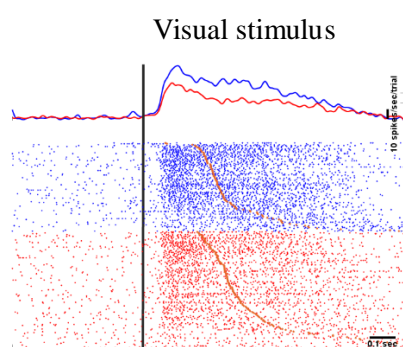
(a) Neuropixels probe
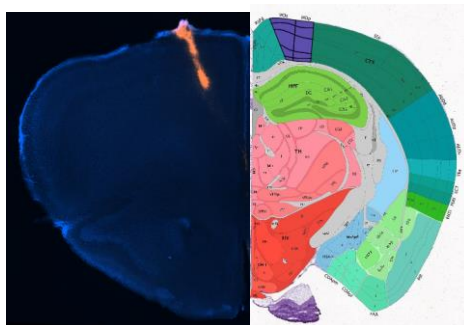
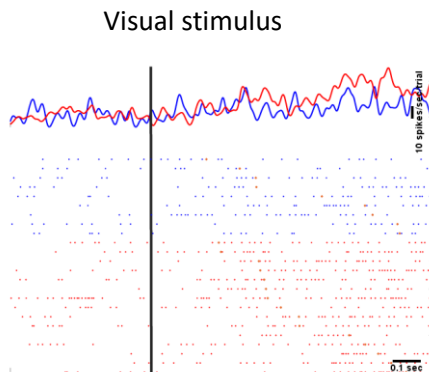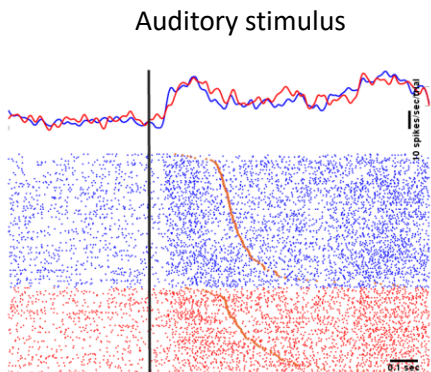(b) Histological picture of mouse brain with probe tract

(c) Example neurons
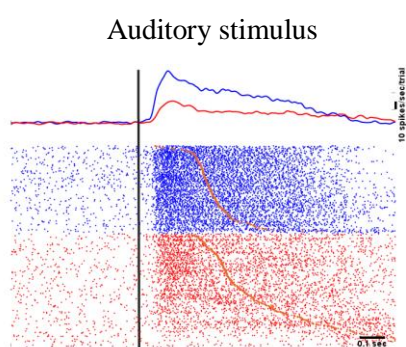
Auditory stimulus

Red - Stimulus on the right
Blue - Stimulus on the left

Visual stimulus

Multimodal neuron

Auditory stimulus

Visual stimulus

Auditory Neuron

Active mode

Passive mode
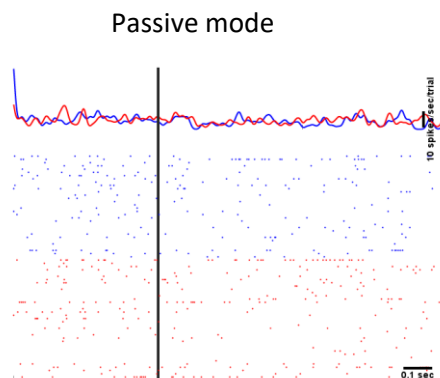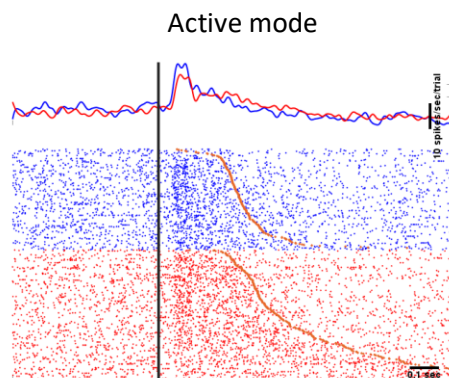

Neuron sensitive to task mode (responding to auditory stimuli)

Fig. 2: High-density electrophysiology recording (a) Structure of a neuropixels probe with the highly dense shank. (modified with permission from Jun *et al.*, 2017). The 9 mm shank is the actual part that is inserted into the brain. There are 960 recording sites along the length of this shank, which allow for well isolated recordings from hundreds of neurons at a time. In my study, we recorded from 394 of these sites. **(b)** Histological section of mouse brain with probe tract marked with a fluorescent dye. The Allen Brain Atlas shows the M1 and M2 highlighted in blue. **(c)** Example neurons sensitive to various stimuli and task conditions. The top subplot shows the average firing rate in spikes/sec/trial. Below that is the spike raster showing the firing patterns of the neuron for each trial, separated by the direction of the stimuli. The individual rows represent each trial. The black bar represents stimulus onset. Within each trial type (red/blue), the trials are sorted by the onset of wheel movement. The orange dots on the spike raster are markers for movement onset. All these recordings, unless otherwise mentioned, are from when the mouse actively performed the task. The example neuron sensitive to task mode is responding to auditory stimuli during active and passive recordings respectively.

From previous work done in our lab, it has been established that performance on the task can be predicted from the stimulus. I wanted to find out if M2 neuronal activity can predict performance better than just stimulus presentations. The first step was to check whether the neurons respond to auditory or visual stimuli and with what frequency. Out of 8166 neurons which were included in passive, 2195 responded to either auditory or visual stimuli. Fig. 3(a) shows that neurons were consistently more responsive to auditory stimuli for all 3 mice. Then, I combined the spiking data with the data from the behavioral task. I analyzed this data using MATLAB to see if there is any correlation between the behavioral decisions of the mice and the activity of the M2 neurons while performing the audio-visual integration task. Fig. 3(b) is a correlation plot between the average change in firing rate for every neuron cluster for auditory and visual stimuli. I did not observe a high correlation ($R^2 = 0.0702$) even though the p value was very highly significant.

In the next two figures (Fig. 3 (c) and 3 (d)), I tried to find out if there were neurons that responded significantly differently to stimuli from the left and right directions, in both active and passive modes. In active mode, 3161 out of 8043 total neurons were responsive to either auditory or visual stimuli. What I found was that the percentage of such cells was generally low for the mice, except for mouse 2 which had 10% and 11% of neurons responding differently to auditory stimuli from the two sides in active and passive recordings respectively (7% and 2.8% for visual stimuli). For an example of such a neuron, see the multimodal neuron in Fig. 2 (c), which responds differently for auditory stimuli from both sides.
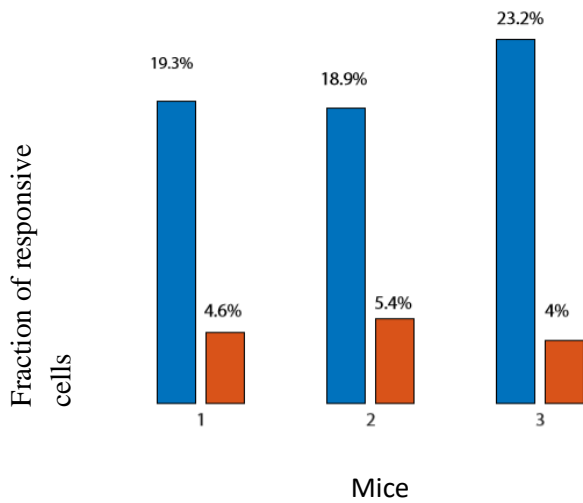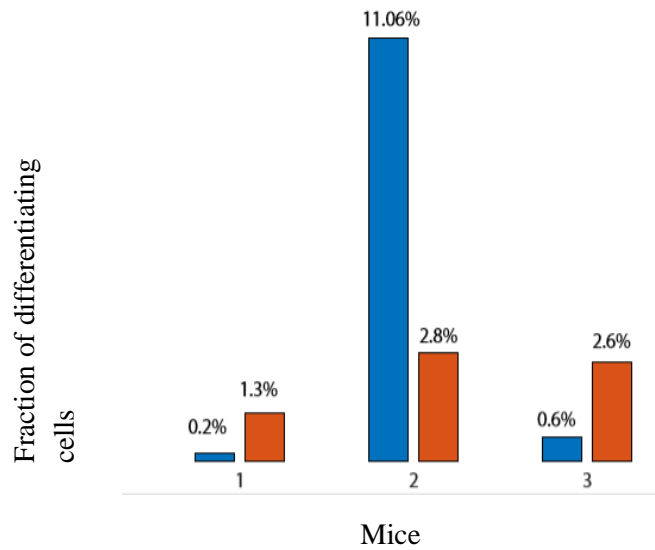
(a) Fraction of cells responsive to auditory (blue) and visual (orange) stimuli in passive
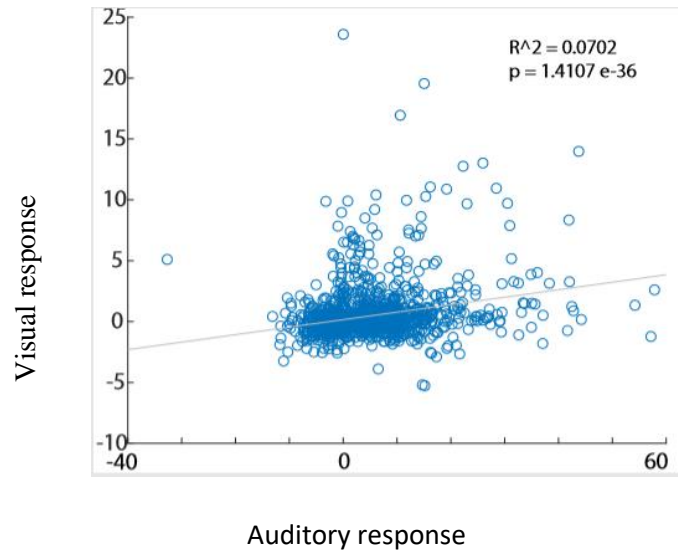
(b) Correlation plot between response to visual and auditory stimuli in passive
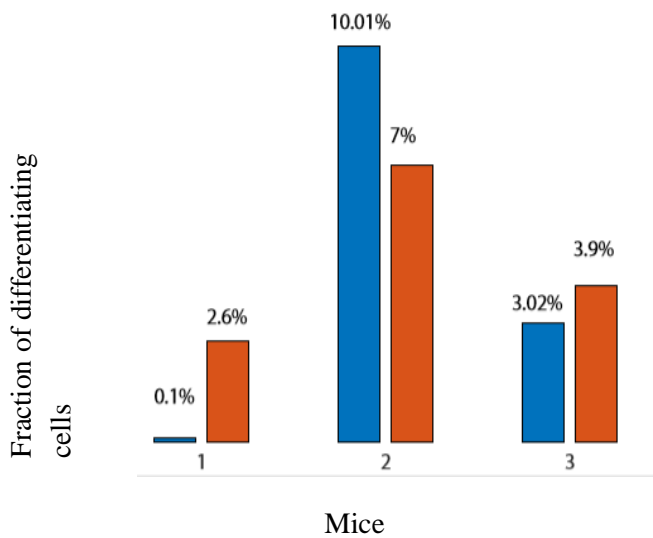
(c) Fraction of cells responding significantly differently to left and right auditory (blue) and visual (orange) stimuli in passive recordings

(d) Fraction of cells responding significantly differently to left and right auditory (blue) and visual (orange) stimuli in active recordings

Fig. 3: Analysing the data (a) Fraction of cells responding to auditory and visual stimuli. The Y-axis is the fraction of responsive cells and on the X-axis are the individual mice, with the neuron clusters divided into auditory (blue) and visual (orange) responsive cells. Paired t-test was used for analysis, with significance level of $p<0.01$. 8166 cells were included in the passive data, out of which 2195 were responsive to either stimulus. **(b)** Correlation plot between response to visual and auditory stimuli. The Y-axis represents the visual responses and the X-axis is the auditory responses. Only the 2195 responsive neurons from the earlier analysis were included. R^2 was 0.0702, indicating low correlation between auditory and visual responsive neurons. **(c) & (d)** Fraction of cells which respond differently to stimuli from the left and right directions. In active, the 3161 responsive neurons were included. Unpaired t-test with significance level of $p<0.01$ was used. (n = 3 mice)

Discussion

I trained 6 mice in a modified version of the 2-AFC task described by Burgess *et al.* (2017). I then recorded from the secondary motor cortices of the trained mice while they performed the task, using neuropixels probes. Then, I analyzed the behavioral and electrophysiological data to build a picture of the role of M2 in multisensory decision making.

We chose to study multisensory integration in mice as they are amenable to a large variety of experimental manipulations. The availability of new, powerful tools such as the Allen Brain Atlas and the Mouse Brain Architecture Project have provided maps of gene expression and brain connectivity that are not available for other species (Carandini and Churchland, 2013). Studies by Raposo *et al.* (2012) and Sheppard, Raposo and Churchland (2013) have shown that rodents combine multisensory information in a statistically optimal manner, like humans. Brunton, Botvinick and Brody (2013) have shown that rodents can accumulate information over time to make decisions based on an abstract quantity.

I chose to focus on the M2 as previous unpublished work in our lab used optogenetics to isolate the M2 as being involved in multisensory integration. While no such studies have been conducted involving M2, there have been some which have reported a role for other areas of the frontal cortex. Uylings, Groenewegen and Kolb (2003) and Kesner and Churchwell (2011) have shown that frontal cortex is necessary for higher cognitive functions in rodents. Other studies have shown that sub-areas such as the orbitofrontal cortex (Kepecs *et al.*, 2008), agranular cortex (Erlich, Bialek and Brody, 2011) and anterior cingulate cortex (Narayanan

and Laubach, 2006) are all involved in various aspects of motor planning and perceptual decision making. Studies by Angelaki, Gu and Deangelis, (2009) and Raposo, Kaufman and Churchland (2014) have reported a role for the posterior parietal cortex (PPC). However, in our optogenetic inactivation experiments, we found no role for the PPC in multisensory integration. Moreover, Raposo, Kaufman and Churchland (2014) themselves found that inactivating the PPC did not impair behavior in multisensory trials.

We chose a 2-AFC task design as it offers key advantages over other methods. Go/no-go tasks are a very popular study design but suffer from a key issue that they are highly vulnerable to changes in the animal's motivation and decision criterion. A decline in performance due to decrease in motivation could be misinterpreted as a failure to identify the relevant stimulus attribute (Carandini and Churchland, 2013). The 2-AFC design solved both these problems as in every choice, subjects must decide regarding the presence or absence of a stimulus attribute. Any bias towards one choice is readily detectable by analyzing the data.

The neuropixels probes themselves offer tremendous advantages over previously available methods of high-density electrophysiology (Jun *et al.*, 2017). They have densely packed recording sites on a small 9 mm shank, which allows for high-spatiotemporal resolution with well isolated spiking units, along with a large volume coverage of brain regions (Harris *et al.*, 2017). These high site count, single shank probes are a massive improvement over existing multi-shank silicon probes (Shobe *et al.*, 2015; Rios *et al.*, 2016; Scholvin *et al.*, 2016). This allows for a small cross-sectional area which minimizes brain tissue damage.

On analyzing the data, I found neurons sensitive to auditory and visual stimuli as well as to the mode of stimulus presentation (active vs. passive). For all mice, neurons were more responsive to auditory than visual stimuli. Also, more neurons were responsive to either stimuli during active recordings, as compared to passive (3161 vs. 2195). This could be because animals are more engaged in the task, with higher motivation for reward, during the active mode. In the active recordings, all trials included an auditory stimulus, in the form of an onset tone. Perhaps, the mice are more sensitive to this stimulus, thus explaining the above effect. This could also be because the spiking data is contaminated with neuronal activity resulting from movement in the active mode. I tried to demarcate its effect on spiking, by using markers for movement onset in the cell raster. The example neurons shown clearly do not respond to movement, but the possibility does remain for the larger set of neurons.

I found a very low correlation between the neurons responding to auditory vs. visual stimuli, suggesting that specificity to one modality is independent of the other. Also, the fraction of cells differentiating between left and right sided stimuli was low in two of the three mice. The one mouse (mouse 2) which had a relatively high percentage was also the best performer during the training and recordings. I generally observed a marked decline in auditory performance after the second surgery (craniotomy). This decline was the least with mouse 2. This suggests that overcoming this limitation of the drop-in auditory performance may improve this number.

In conclusion, my studies have started to shed light on the possible mechanisms of how the M2 is involved in audiovisual integration. This project shall be continued in the lab by Dr. Philip Coen, as a part of his larger project of modelling the

activity of M2 in multisensory decision making. Further analysis can be carried out on the already collected dataset, looking at the reaction times of the mice to auditory and visual stimuli and for correlations between neurons that differentiate between left and right sided stimuli. The change in neural responses to high contrast vs. low contrast visual stimuli can also be looked at. We also aim to find out the effect of the performance of the mice in various sessions on the responsiveness of the neurons and on the number of timed-out trials. These would give us a better idea of neuronal activity in the frontal cortex during this task.

Limitations of methods

One very prominent limitation in our study was the marked decline in performance in auditory trials following the craniotomy. This probably did affect the spiking activity of the neurons and prevents us from getting a complete picture of any possible correlations in the responses. We tried to overcome this by removing the ear-bars used during the surgery. Following this, the auditory performance did improve slightly, but the results were still not satisfactory. So, this is something that will require more efforts to solve.

Another limitation was the rapid re-growth of bone and scar tissue in and around the craniotomy. This greatly restricted the time available to us to record from the mice, before another craniotomy was needed, or the mouse had to be culled. We have tried various methods in the lab, such as placing a honeycomb disc around the borders of the craniotomy, to try and slow the growth, but none have been effective so far.

Acknowledgements

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