MULTIMODAL MISMATCH RESPONSES IN MOUSE AUDITORY CORTEX

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SUMMARY

Our movements result in predictable sensory feedback that is often multimodal. Based on deviations between predictions and actual sensory input, primary sensory areas of cortex have been shown to compute sensorimotor prediction errors. How prediction errors in one sensory modality influence the computation of prediction errors in another modality is still unclear. To investigate multimodal prediction errors in mouse auditory cortex (ACx), we used a virtual environment to experimentally couple running to both self-generated auditory and visual feedback. Using two-photon microscopy, we first characterized responses of layer 2/3 (L2/3) neurons to sounds, visual stimuli, and running onsets and found responses to all three stimuli. Probing responses evoked by audiomotor mismatches, we found that they closely resemble visuomotor mismatch responses in visual cortex (V1). Finally, testing for cross modal influence on audiomotor mismatch responses by coupling both sound amplitude and visual flow speed to the speed of running, we found that audiomotor mismatch responses were amplified when paired with concurrent visuomotor mismatches. Our results demonstrate that multimodal and non-hierarchical interactions shape prediction error responses in cortical L2/3.

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INTRODUCTION

Neuronal responses consistent with prediction errors have been described in a variety of different cortical areas (Audette and Schneider, 2023; Ayaz et al., 2019; Han and Helmchen, 2023; Heindorf et al., 2018; Keller et al., 2012; Liu and Kanold, 2022) and across different species (Eliades and Wang, 2008; Keller and Hahnloser, 2009; Stanley and Miall, 2007). In V1, these responses are thought to be learned with experience (Attinger et al., 2017) and depend on local plasticity in cortex (Widmer et al., 2022). Prediction errors signal the unanticipated appearance or absence of a sensory input, and are thought to be computed as a deviation between top-down predictions and bottom-up sensory inputs (Rao and Ballard, 1999). One

type of top-down signals that conveys a prediction of sensory input are motor-related signals (Leinweber et al., 2017). In auditory cortex, motor-related signals can modulate responses to self-generated vocalizations (Eliades and Wang, 2008) or to sounds coupled to locomotion (Schneider et al., 2018). Auditory cortex is thought to use these motor-related signals to compute audiomotor prediction error responses (Audette et al., 2022; Audette and Schneider, 2023; Eliades and Wang, 2008; Keller and Hahnloser, 2009; Liu and Kanold, 2022). These audiomotor prediction errors can be described in a hierarchical variant of predictive processing, in which top-down motor-related signals function as predictions of bottom-up sensory input. While parts of both auditory and visual processing streams are well described by a hierarchy, the cortical network as a whole does not easily map onto a hierarchical architecture, anatomically (Markov et al., 2013) or functionally (St-Yves et al., 2023; Suzuki et al., 2023), in a non-trivial way. One of the connections that does not neatly fit into a hierarchical model is the surprisingly dense reciprocal connection between ACx and V1 (Clavagnier et al., 2004; Falchier et al., 2002; Ibrahim et al., 2016; Leinweber et al., 2017; Zhao et al., 2022). From ACx to V1 this connection conveys a prediction of visual input given sound (Garner and Keller, 2022). What the reciprocal projection from V1 to ACx conveys, is still unclear. In proposals for hierarchical implementations of predictive processing there are no such lateral connections, and there is no reason to assume prediction error computations in different modalities should directly interact at the level of primary sensory areas. Thus, we argued that the lateral interaction between V1 and ACx is a good starting point to investigate how non-hierarchical interactions are involved in the computation of prediction errors, and how multimodal interactions shape sensorimotor prediction errors.

Based on this idea, we designed an experiment in which we could couple and transiently decouple running speed in a virtual environment to both self-generated auditory feedback and self-generated visual flow feedback. While doing this, we recorded activity in L2/3 neurons of ACx using two-photon calcium imaging. Using this approach, we first confirmed that a substantial subset of L2/3 neurons in ACx responds to either auditory, visual (Sharma et al., 2021), or motor-related inputs (Henschke et al., 2021; Morandell et al., 2023; Vivaldo et al., 2023). While we found that L2/3 neurons in ACx responded to audiomotor mismatches in a way that closely resembles visuomotor mismatch responses found in V1 (Keller et al., 2012), we found no evidence of responses to visuomotor mismatch in ACx. However, when coupling both visual flow and auditory feedback to running, we found that L2/3 neurons in ACx non-linearly combine information about visuomotor and audiomotor mismatches. Overall, our results demonstrate that prediction errors can be potentiated by multimodal interactions in primary sensory cortices.

RESULTS

Auditory, visual, and motor-related signals were intermixed in L2/3 of ACx.

To investigate auditory, visual, and motor-related signals in mouse ACx, we combined an audiovisual virtual reality system with two-photon calcium imaging in L2/3 ACx neurons (**Figure 1A**). We used an adeno-associated viral (AAV) vector to express a genetically encoded calcium indicator (AAV2/1-EF1α-GCaMP6f-WPRE) in ACx (**Figures 1B-D**). Following recovery from surgery, mice were habituated to the virtual reality setup (**Figure 1C**). We first mapped the location of the primary auditory cortex (A1) and the anterior auditory field (AAF) using widefield calcium imaging (**Figure 1C and Figure 1E**). Based on these maps, we then chose recording locations for two-photon imaging of L2/3 neurons in either A1 or AAF. For the purposes of this work, we did not distinguish between A1 and AAF and will refer to these two areas here as ACx. To characterize basic sensory and motor-related responses, we recorded neuronal responses to pure tones, full-field moving gratings, and running onsets. We first assessed population responses of L2/3 neurons evoked by sounds (pure tones presented at 4 kHz, 8 kHz, 16 kHz, or 32 kHz at either 60 dB or 75 dB sound pressure level (SPL); **Figure 1F**). While pure tones resulted in both increases or decreases in calcium activity in individual neurons (**Figure 1G**), the average population response exhibited a significant decrease in activity (**Figure 1H**). Next, we analyzed visual responses evoked by full-field drifting gratings (see Methods; **Figure 1I**). Visual stimulation resulted in a diverse response across the population of L2/3 neurons (**Figure 1J**) that was initially positive at the population level (**Figure 1K**). To quantify motor-related inputs, we analyzed activity during running onsets (**Figure 1L**). We found that the majority of neurons increased their activity during running onsets (**Figure 1M**), which was also reflected in a significant positive response on the population level (**Figure 1N**). Finally, we investigated how running modulates auditory and visual responses in ACx. In V1, running strongly increases responses to visual stimuli (Niell and Stryker, 2010), while in auditory cortex running has been shown to modulate auditory responses in a variety of different ways (Audette et al., 2022; Bigelow et al., 2019; Henschke et al., 2021; McGinley et al., 2015; Morandell et al., 2023; Schneider et al., 2014; Vivaldo et al., 2023; Yavorska and Wehr, 2021; Zhou et al., 2014). Separating auditory responses by running state, we found that sound evoked responses of ACx neurons were overall similar during sitting and running, but exhibited a smaller decrease in activity when the mouse was sitting (**Figure S1A**). Visual responses also appeared overall similar but with a small increase in strength during running (**Figure S1B**), similar to the running modulation effect observed on visual responses in V1. Thus, running appears to moderately and differentially

modulate auditory and visual responses in L2/3 ACx neurons. Consistent with previous work, these results demonstrate that auditory, visual, and motor-related signals are all present in ACx and that running modulation influences L2/3 ACx neurons differently than in V1.

L2/3 neurons in ACx responded to audiomotor mismatch.

To test whether auditory, visual, and motor-related signals are integrated in L2/3 neurons of ACx to compute prediction errors, we first probed for responses to audiomotor (AM) mismatches. A mismatch in this context, is the absence of a sensory input that the brain predicts to receive from the environment, and thus a specific type of negative prediction error. We experimentally generated a coupling between movement and sensory feedback and then used movement as a proxy for what the mouse predicts to receive as sensory feedback. To do this with an auditory stimulus, we coupled the sound amplitude of an 8 kHz pure tone to the running speed of the mouse on the spherical treadmill such that sound amplitude was proportional to locomotion speed (**Figures 2A and 2B).** In this paradigm, a running speed of 0 corresponded to a sound amplitude of 0, while 30 cm/s running speed corresponded to a sound amplitude of 60 dB SPL. We refer to this type of session as closed loop. We then introduced AM mismatches by setting the sound amplitude to 0 for 1 s at random times (on average every 15 s). An alternative approach to introduce AM mismatches would have been to clamp the sound amplitude to a constant value. However, based on the analogy between sound amplitude and visual flow speed in visuomotor (VM) mismatch paradigms, where we induce VM mismatch by setting visual flow speed to 0 (Keller et al., 2012), we chose the former. We found that AM mismatch resulted in a strong population response (**Figure 2C and Figure 2D**). Interestingly, this response was already apparent in the first closed loop session with audiomotor coupling that the mice ever experienced, suggesting that this coupling is learned very rapidly (**Figure S2A**). To test whether AM mismatch responses can be explained by a sound offset response, we performed recordings in open loop sessions that consisted of a replay of the sound profile the mouse had self-generated in the preceding closed loop session. Mice were free to run during this session and did so at similar levels as during the closed loop session (**Figure S2B**). The average response to the playback of sound halt during the open loop session was significantly less strong than the average response to AM mismatch (**Figure 2D**), but in contrast to visual playback halt responses in V1 (Vasilevskaya et al., 2023), we found no evidence of a running modulation of the response to the playback halt (**Figure S2C**). Thus, L2/3 neurons in ACx respond to AM mismatch in a way similar to how the L2/3 neurons in V1 respond to visuomotor (VM) mismatch.

Assuming that AM mismatch responses are computed as a difference between an excitatory motor-related prediction and an auditory stimulus driven inhibition, we would expect the neurons with high AM mismatch responses to exhibit opposing influence of motor-related and auditory input. To test this, we selected the 5% of neurons with the strongest responses to AM mismatch and quantified the responses of these neurons to sound stimulation and running onsets. Consistent with a model of a subtractive computation of prediction errors, we found that AM mismatch neurons exhibited a strong reduction in activity in response to sound stimulation and an increase of activity on running onsets (**Figure 2E**). Given that mismatch responses are likely enriched in the superficial part of L2/3 (O'Toole et al., 2023), and that in our two-photon imaging experiments we also preferentially recorded from more superficial neurons, we suspect that our population is enriched for mismatch neurons. Consistent with this interpretation, we observed a strong population response to AM mismatches (**Figures 2C and 2D**) and a decrease in population activity in response to sound stimulation (**Figure 1H**). Nevertheless, sound evoked responses were significantly more negative in neurons strongly responsive to AM mismatch, than for the remainder of the L2/3 neuronal population (**Figure 2F**). This effect was similar when we used different thresholds for the selection of AM mismatch neurons (10% or 20% of neurons with the strongest response to AM mismatch; **Figure S3**). Consistent with a sound driven reduction of activity and running related increase of activity in AM mismatch neurons, the correlation of calcium activity of AM mismatch neurons was predominantly negative with sound amplitude and positive with running speed in open loop sessions (**Figure 2G**). This again resembles the properties of VM mismatch neurons in V1 (Attinger et al., 2017). If AM mismatch responses are computed as a difference between a locomotion driven excitation and a sound driven inhibition, we could also expect to find a correlation between the strength of mismatch response and the strength of sound playback halt responses. Even in the absence of locomotion driven excitation, a relief from sound driven inhibition could trigger an increase in calcium activity. When comparing AM mismatch responses with playback sound halt responses for all neurons, we do indeed find a positive correlation between the two (**Figure 2H**). Overall, these results suggest that the implementation of sensorimotor prediction error computation generalizes beyond V1 to other primary cortices and might be a canonical cortical computation in L2/3.

We found no evidence of visuomotor mismatch responses in L2/3 of ACx.

Visuomotor mismatch responses are likely calculated in V1 (Jordan and Keller, 2020), and spread across dorsal cortex from there (Heindorf and Keller, 2023). To investigate multimodal mismatch responses, we

150 first quantified the strength of these VM mismatch responses, which are independent of auditory input,
151 in ACx. In these experiments, the running speed of the mouse was coupled to the visual flow speed in a
152 virtual corridor, but not to any sound feedback (**Figures 3A and 3B**). We introduced VM mismatches by
153 halting visual flow for 1 s at random times while the mice were running, as previously described (Keller et
154 al., 2012; Zmarz and Keller, 2016). To control for visual responses independent of visuomotor coupling,
155 we used an open loop replay of the visual flow generated in the previous session (see Methods). We found
156 that neither VM mismatches nor visual flow playback halts, which the mouse experienced in open loop
157 sessions, resulted in a measurable population response in ACx (**Figures 3C and 3D**). Selecting the 5% of
158 neurons with the strongest responses to VM mismatches and quantifying their responses to grating
159 presentations and running onsets, we found that these neurons exhibited positive responses to running
160 onset and no significant response to grating stimuli (**Figure 3E**). These responses were not different from
161 the population responses of the remainder of the neurons (**Figure 3F**). Quantifying the correlation of
162 calcium activity with visual flow speed and running speed in the open loop session, we found that VM
163 mismatch responsive neurons exhibited a distribution not different from chance (**Figure 3G**). We also
164 found no evidence of a correlation between VM mismatch responses and playback halt responses (**Figure**
165 **3H**). Thus, while there may be a small subset of VM mismatch responsive neurons in L2/3 of ACx, we find
166 no evidence of a VM mismatch response at the level of the L2/3 population.

167 **Mismatch responses were potentiated by multimodal interactions.**

168 Finally, we explored how multimodal coupling of both auditory and visual feedback to running speed
169 influenced mismatch responses in L2/3 of ACx. To do this, we coupled both sound amplitude and visual
170 flow speed to the running speed of the mouse in an audiovisual virtual environment (**Figures 4A and 4B**).
171 We then introduced mismatch events by halting both sound and visual flow for 1 s to trigger a concurrent
172 audiomotor and visuomotor [AM + VM] mismatch (**Figure 4B**). The nomenclature here is such that the
173 first letter in the pair denotes the sensory input that is being predicted, while the second letter denotes
174 the putative predictor – the square brackets are used to denote that the two events happen concurrently.
175 By putative predictor, we mean an information source available to the mouse that would, in principle,
176 allow it to predict another input, given the current experimental environment. Thus, in the case of a [AM
177 + VM] mismatch both the halted visual flow and the halted sound amplitude are predicted by running
178 speed. The [AM + VM] mismatch resulted in a significant response on the population level (**Figure 4C**). The
179 concurrent experience of mismatch between multiple modalities could simply be the result of a linear

combination of the responses to the different mismatch stimuli or could be the result of a non-linear combination. To test whether we find evidence of a non-linear combination of mismatch responses, we compared the [AM+VM] mismatch to [AM] and [VM] mismatch events presented alone. We found that the presentation of a [AM+VM] mismatch led to a significantly larger response than either an [AM] or a [VM] mismatch in isolation (**Figure 4D**). To test whether the linear summation of [AM] + [VM] mismatch responses could explain the response to the concurrent presentation [AM+VM], we compared the two directly, and found that the concurrent presentation [AM+VM] elicited a significantly larger response than the linear sum of [AM] + [VM] mismatch responses (**Figures 4E and S4**). Plotting the [AM+VM] mismatch responses against the linear sum of the [AM] + [VM] mismatch responses for each neuron, we found that while there is some correlation between the two, there is a subset of neurons (13.7%; red dots, **Figure 4F**) that selectively respond to the concurrent [AM+VM] mismatch, while a different subset of neurons (11.2%; orange dots, **Figure 4F**) selectively responds to the mismatch responses in isolation. This demonstrates that mismatch responses in different modalities can interact non-linearly.

DISCUSSION

Consistent with previous reports, we found that auditory, visual, and motor-related signals are intermixed in the population of L2/3 neurons in ACx. Responses to both motor-related (McGinley et al., 2015; Schneider et al., 2014; Vivaldo et al., 2023; Yavorska and Wehr, 2021; Zhou et al., 2014) and visual signals (Bigelow et al., 2022; Morrill and Hasenstaub, 2018; Sharma et al., 2021) have been reported across layers in ACx, with the strongest running modulation effect found in L2/3 (Schneider et al., 2014). Also, consistent with previous reports, we found that a subset of L2/3 neurons in ACx respond to audiomotor prediction errors (Audette et al., 2022; Liu and Kanold, 2022). In V1, it has been demonstrated that neurons signaling prediction errors exhibit opposing influence of bottom-up visual and top-down motor-related inputs. This has been speculated to be the consequence of a subtractive computation of prediction errors (Jordan and Keller, 2020; Keller et al., 2012; Leinweber et al., 2017). Our findings now reveal a similar pattern of opposing influence in prediction error neurons in primary ACx that exhibit a positive correlation with motor-related input and a negative correlation with auditory input (**Figure 2G**). This would be consistent with the idea that both visuomotor and audiomotor prediction errors are computed as a subtractive difference between bottom-up and top-down inputs. Based on this, it is conceivable that this type of computation extends also beyond primary sensory areas of cortex and may be a more general computational principle implemented in L2/3 of cortex.

Finally, we found that concurrent prediction errors in multiple modalities result in an increase in prediction error response that exceeds a linear combination of the prediction error responses in single modalities (**Figure 4E**), with a subset of neurons selectively responding only to the combination of prediction error responses (**Figure 4F**). A similar non-linear relationship has been described between auditory and visual oddball responses in both ACx and V1 (Shiramatsu et al., 2021). At this point, it should be kept in mind that deviations from linearity in terms of spiking responses are difficult to assess using calcium imaging data. However, given that the difference between the concurrent presentation and the linear sum of the two individual mismatch responses was approximately a factor of two (**Figure 4E**), and the fact that we found a population of neurons that responds selectively to the concurrent presentation of both mismatches, we suspect that also the underlying spiking responses are non-linear. What are the mechanisms that could underlie this interaction? Neurons in ACx have access to information about VM mismatches from at least two sources. In widefield calcium imaging, VM mismatch responses are detectable across most of dorsal cortex (Heindorf and Keller, 2023). Thus, VM mismatch responses could be present in long-range cortico-cortical axons from V1, or possibly in L4, L5, or L6 neurons in ACx. Alternative sources of VM mismatch input are neuromodulatory signals. Locus coeruleus, for example, drives noradrenergic signals in response to VM mismatches across the entire dorsal cortex (Jordan and Keller, 2023). However, given that noradrenergic signals only weakly modulate responses in L2/3 neurons in V1 (Jordan and Keller, 2023), it is unclear if the broadcasted noradrenergic signals could non-linearly potentiate the AM mismatch responses of ACx neurons. We speculate that cholinergic signals are also unlikely to contribute to this effect. In V1 there are no cholinergic responses to VM mismatch (Yogesh and Keller, 2023). However, given that ACx and V1 receive cholinergic innervation from different sources (Kim et al., 2016), we cannot rule out the possibility that cholinergic signals in ACx respond to VM mismatch. Nevertheless, given that the [AM+VM] mismatch responses do not simply appear to be an amplified variant of the [AM] mismatch responses (**Figure 4F**), we speculate that [AM+VM] mismatch responses are primarily driven by long-range cortico-cortical input from V1 that interacts with a local computation of [AM] mismatch responses in the L2/3 ACx circuit.

Lateral interactions in the computation of prediction errors between sensory streams are not accounted for by hierarchical variants of predictive processing. In these hierarchical variants, prediction errors are computed as a comparison between top-down and bottom-up inputs (Rao and Ballard, 1999). To explain the lateral interactions between prediction errors likely computed in ACx (AM mismatch responses) and prediction errors likely computed in V1 (VM mismatch responses) that we describe here, we will need

new variants of predictive processing models that include lateral and non-hierarchical interactions. Thus, our results demonstrate that mismatch responses in different modalities interact non-linearly and can potentiate each other. The circuit mechanisms that underlie this form of multimodal integration of mismatch responses are still unclear and will require further investigation. However, we would argue that the relatively strong multimodal interaction demonstrates that unimodal and hierarchical variants of predictive processing are insufficient to explain cortical mismatch responses - if predictive processing aims to be a general theory of cortical function, we will need to explore non-hierarchical variants of predictive processing.

FIGURES

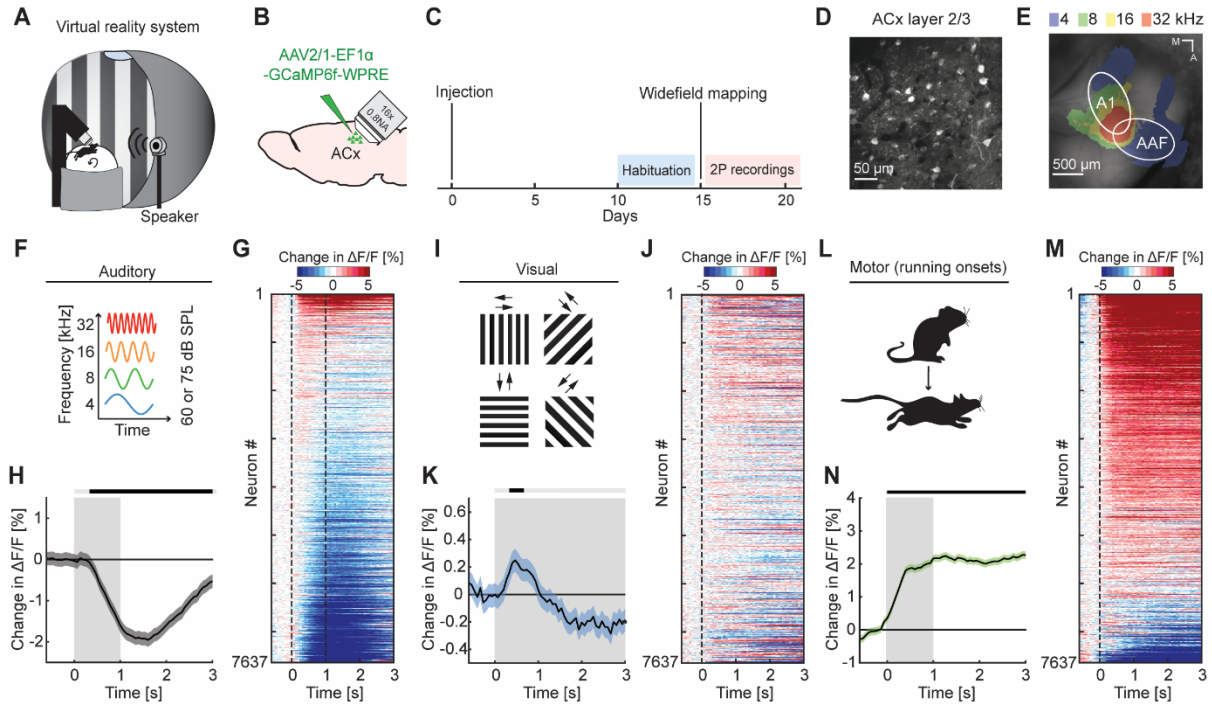

Figure 1. Auditory, visual, and motor-related signals were present in L2/3 of ACx.

(**A**) Schematic of the virtual reality system. For imaging experiments, mice were head-fixed and free to run on an air-supported spherical treadmill. For all recordings, the microscope was tilted 45 degrees to the left to image left ACx.

(**B**) Strategy for two-photon imaging of L2/3 ACx neurons. We injected an AAV vector to express a genetically encoded calcium indicator in ACx.

(**C**) Timeline of the experiment. Starting 10 days after viral injection and window-implantation surgery mice were habituated to the virtual reality setup without any visual or auditory stimulation for 5 days. We mapped ACx with widefield imaging to be able to target two-photon (2P) imaging to ACx. In 1 to 6 recording sessions, 1 session per day, we recorded from 7637 neurons in 17 mice.

(**D**) Example two-photon image in L2/3 of ACx.

(**E**) Example widefield mapping of ACx. Response maps reflect regions with the strongest response for each tested sound frequency.

(**F**) The sound stimuli were 1 s long pure tones of 4 kHz, 8 kHz, 16 kHz, or 32 kHz played at 60 dB or 75 dB sound pressure level (SPL), presented with randomized inter-stimulus intervals.

(**G**) The average sound evoked response of all L2/3 ACx neurons across all tested frequencies and sound levels. Sound is presented from 0 s to 1 s. Red indicates an increase in activity, while blue indicates a decrease in activity. All responses are baseline subtracted. To avoid regression to the mean artifacts in plotting, the response heatmap is generated by splitting data in two halves by trials. The responses from the first half of trials are used to sort neurons by response strength and the average responses of the

273 second half of trials are plotted for each neuron. To prevent graphical aliasing, the heatmaps are
274 smoothed over 10 neurons for plotting.

275 (**H**) The average sound evoked population response of all ACx L2/3 neurons across all tested frequencies
276 and sound levels (7637 neurons). Stimulus duration was 1 s (gray shading). Here and in subsequent panels,
277 solid black lines represent mean and shading SEM. The horizontal bar above the plot marks time bins in
278 which the response is statistically different from 0 (gray: not significant, black: $p<0.05$; see Methods).

279 (**I**) The visual stimuli we used were full-field drifting gratings of 8 different directions, presented for 4 s to
280 8 s with randomized inter-stimulus intervals.

281 (**J**) As in **G**, but for gratings onsets responses averaged across all orientations.

282 (**K**) As in **H**, but for the population response to grating onsets averaged across all orientations.

283 (**L**) Motor-related activity was assessed based on responses upon running onsets.

284 (**M**) As in **G**, but for running onset responses.

285 (**N**) As in **H**, but for the average population response to running onsets. Only data from running onsets in
286 which the mouse ran for at least 1 s (gray shading) were included.

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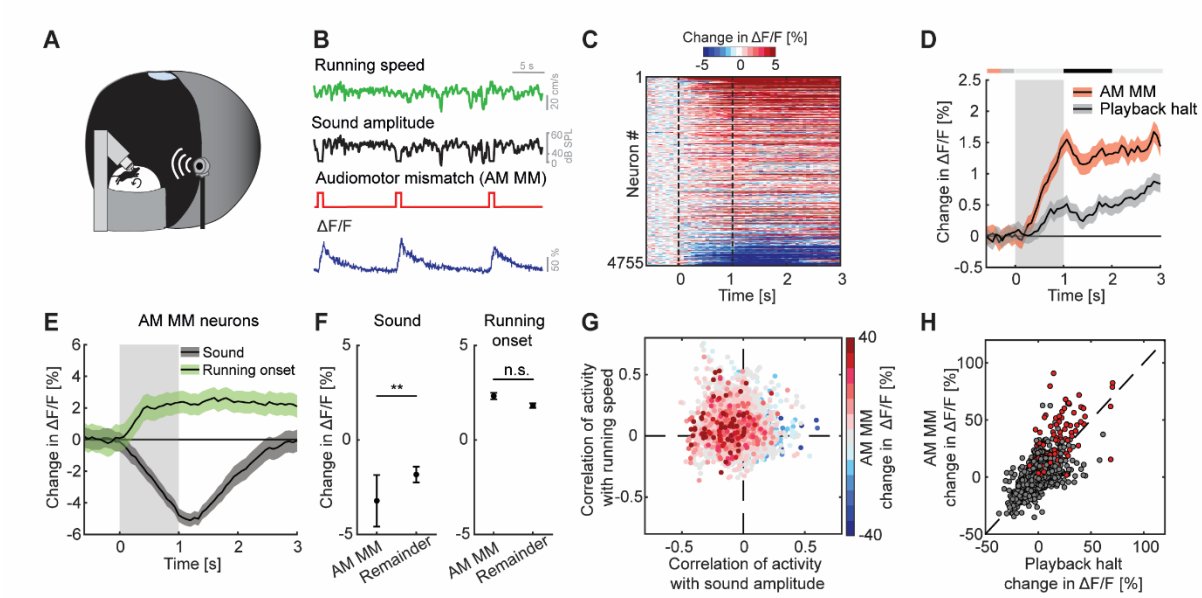


Figure 2. L2/3 neurons of ACx responded to audiomotor mismatch events.

(**A**) Schematic of the virtual reality system used to study responses to audiomotor (AM) mismatches. The sound amplitude of an 8 kHz pure tone was coupled to the running speed of the mouse on a spherical treadmill. These experiments were performed in darkness.

(**B**) In closed loop sessions, the running speed of the mouse was coupled to the sound amplitude. AM mismatches were introduced by briefly setting the sound amplitude to 0 for 1 s. Below, the calcium response of an example neuron to AM mismatch events.

(**C**) Responses of all L2/3 ACx neurons to audiomotor mismatches. The response heatmap is generated as described in **Figure 1G**.

(**D**) The average population response of all L2/3 neurons to AM mismatches and sound playback halts (4755 neurons). AM mismatch duration was 1 s (gray shading). The horizontal bar above the plot marks time bins in which the AM mismatch response is statistically different from the playback halt response (gray: not significant., black: $p<0.05$; see Methods).

(**E**) The average population response of AM mismatch neurons (5% of strongest responders) to sound stimulation (black) and running onsets (green). Sound stimulation was 1 s (gray shading).

(**F**) Comparison of the response strength of AM mismatch (MM) neurons to sound stimulation (left) and running onsets (right) compared to those of the remainder of the neuron population. Error bars indicate SEM. Here and elsewhere, n.s.: not significant; *: $p<0.05$; **: $p<0.01$; ***: $p<0.001$. See Table S1 for all statistical information.

(**G**) Scatter plot of the correlations of calcium activity with sound amplitude (x-axis) and running speed (y-axis) in open loop sessions, for all neurons. The color-code reflects the strength of responses to AM mismatch in the closed loop session. Note, AM mismatch-responsive neurons are enriched in the upper left quadrant.

(**H**) Scatter plot of the responses to AM mismatch and sound playback halt for all neurons. Neurons that exhibited significant ($p < 0.05$) positive responses to AM mismatch are shown in red (13.7%). Black dashed line marks unity.

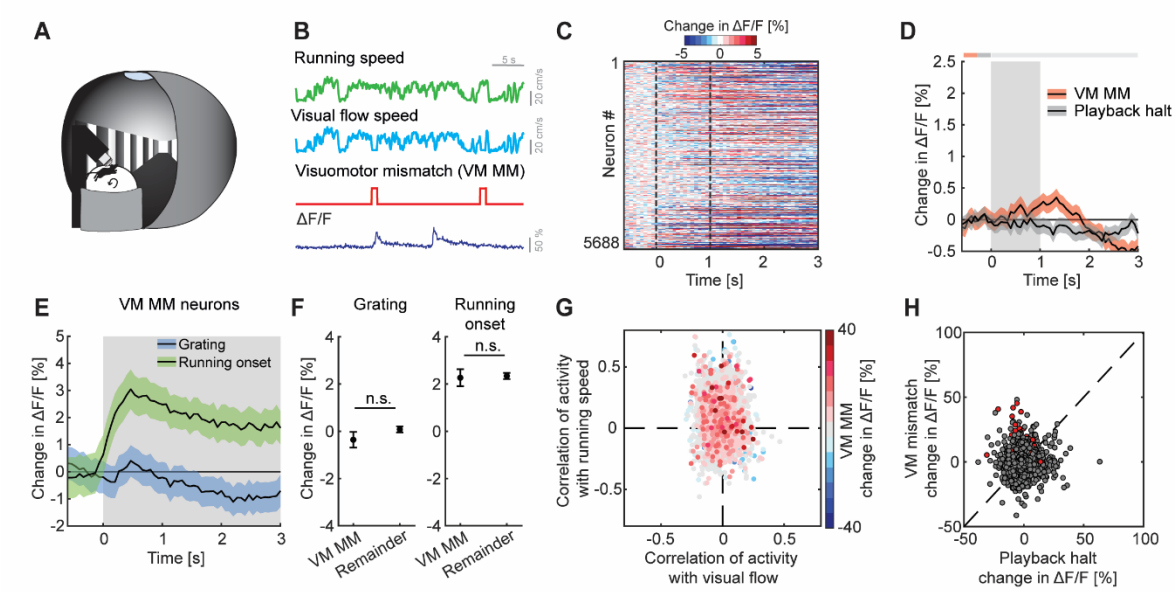


Figure 3. We found no evidence of visuomotor mismatch responses in ACx.

(**A**) Schematic of the virtual reality system used to measure VM mismatch responses. The visual flow of the virtual corridor was coupled to the running speed of the mouse on a spherical treadmill. There was no sound stimulus present in these experiments.

(**B**) In closed loop sessions, the running speed of the mouse was coupled to the movement in a virtual corridor. VM mismatches were introduced by briefly setting visual flow speed to 0 for 1 s. Below, the calcium response of an example neuron to VM mismatch events.

(**C**) Responses of all L2/3 ACx neurons to VM mismatches. The response heatmap is generated as described in **Figure 1G**.

(**D**) The average population response of all L2/3 neurons to VM mismatches and visual flow playback halts (5688 neurons). Gray shading marks the duration of both stimuli. The horizontal bar above the plot marks time bins in which the VM mismatch response is statistically different from the playback halt response (gray: n.s., black: $p<0.05$; see Methods).

(**E**) The average population response of VM mismatch neurons (5% of strongest responders) to grating stimulation (blue) and running onsets (green). Stimulus duration was 4 s to 8 s (gray shading).

(**F**) Comparison of the response strength of VM mismatch (MM) neurons to visual stimulation (left) and running onsets (right) compared to those of the remainder of the neuron population. Error bars indicate SEM. Here and elsewhere, n.s.: not significant; *: $p<0.05$; **: $p<0.01$; ***: $p<0.001$. See Table S1 for all statistical information.

(**G**) Scatter plot of the correlation of calcium activity with visual flow speed (x-axis) and running speed (y-axis) in open loop sessions for all neurons. The color-code reflects the strength of responses to VM mismatch in the closed loop session. Note, VM mismatch responsive neurons are scattered randomly.

(**H**) Scatter plot of the responses to VM mismatch and visual flow playback halt for all neurons. The percentage of neurons (6.6%; in red) that exhibited significant ($p < 0.05$) responses to VM mismatches, is only barely above chance.

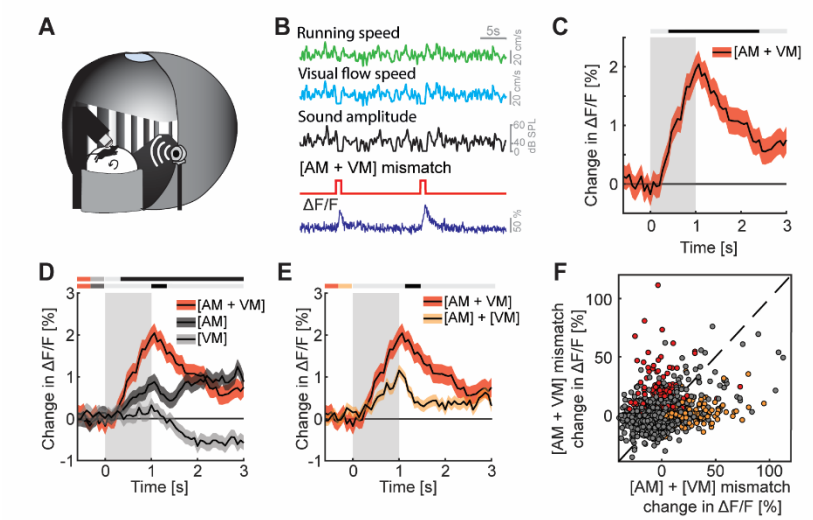


Figure 4. Mismatch responses were potentiated by multimodal interactions in L2/3 ACx neurons.

(**A**) Schematic of the virtual reality system used to measure multimodal mismatch responses. Both the sound amplitude of an 8 kHz pure tone and the movement of the virtual corridor were coupled to the running speed of the mouse on a spherical treadmill.

(**B**) Concurrent audiomotor and visuomotor [AM + VM] mismatches were introduced by simultaneously setting both sound amplitude and visual flow speed to 0 for 1 s.

(**C**) The average population response of all L2/3 ACx neurons to concurrent [AM + VM] mismatches (3289 neurons). Gray shading marks the duration of the mismatch stimulus. The horizontal bar above the plot marks time bins in which the [AM + VM] mismatch response is statistically different from 0 (gray: n.s., black: $p<0.05$; see Methods).

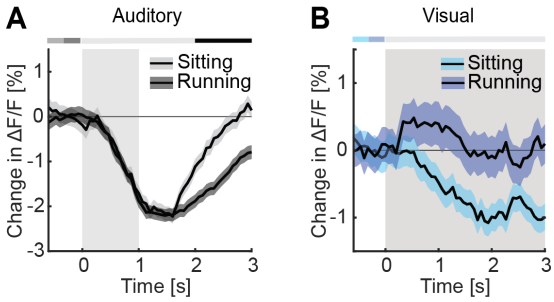
(**D**) Average population response of all L2/3 neurons to concurrent [AM + VM] mismatch and responses evoked by [AM] and [VM] mismatches presented in isolation (same data as shown in **Figures 2 and 3** but sub-selected to match the neurons that were recorded in both unimodal and multimodal mismatch paradigms; 3289 neurons). The horizontal bars above the plot mark time bins in which the [AM + VM] mismatch response is larger than the [AM] or the [VM] mismatch response (gray: n.s., black: $p<0.05$; see Methods). The two short horizontal color bars to the left of time 0 indicate which two responses are being compared. Gray shading indicates the duration of the stimulus.

(**E**) Average population response of all L2/3 neurons to a concurrent [AM + VM] mismatches compared to the linear sum of the responses evoked by [AM] and [VM] mismatches presented in isolation. Gray shading indicates the duration of the stimuli.

(**F**) Scatter plot of the responses of all neurons to the concurrent [AM + VM] mismatches against the linear sum of the responses evoked by [AM] and [VM] mismatches presented in isolation. In red, the subset of neurons (13.7%) that exhibited selective responses to the concurrent [AM+VM] mismatch, and in orange, the subset of neurons (11.2%) in which the linear sum of the responses to [AM] + [VM] mismatches presented in isolation was significant, while response to their concurrent presentation was not. Neurons without a significant response, or that are responsive to both, are shown in gray.

370 **SUPPLEMENTARY FIGURES**

371



372

373 **Figure S1. Running exhibited differential effects on the responses to sound presentation and moving**
374 **grating onsets. Related to Figure 1.**

375 (**A**) The average population response of ACx L2/3 neurons to sound presentation (4390 neurons) during
376 sitting (light gray) and running (dark gray). Stimulus duration was 1 s (gray shading). The horizontal bar
377 above the plot marks time bins in which the responses are statistically different from each other (gray:
378 n.s., black: $p<0.05$; see Methods).

379 (**B**) As in **A**, but for responses to moving gratings (3701 neurons) during sitting (light blue) and running
380 (dark blue). Stimulus duration was 4 s to 8 s (gray shading).

381

382

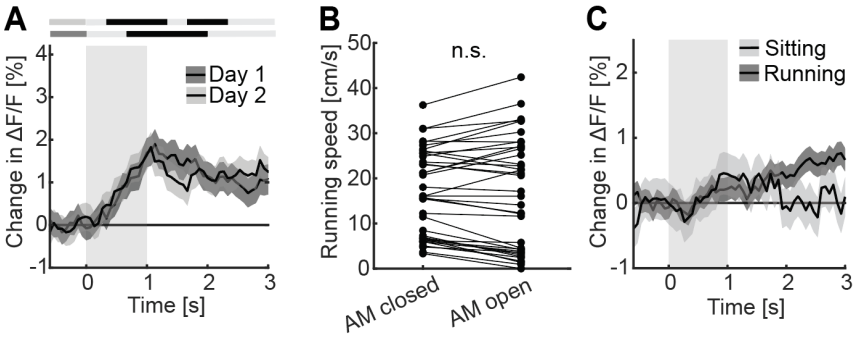


Figure S2. Controls for audiomotor mismatch responses. Related to Figure 2.

(**A**) The average population response of L2/3 ACx neurons to AM mismatches as a function of experience with audiomotor coupling. AM mismatch duration was 1 s (gray shading). The data shown are from the first two audiomotor closed loop sessions. Each closed loop session lasted 5.5 minutes and mice experienced one such session per day (Day 1: 1271, Day 2: 904). Note, AM mismatch responses are already present in the first closed loop session.

(**B**) Comparison of running speeds during either closed or open loop audiomotor sessions. Dots are different recording sessions. Here and elsewhere, n.s.: not significant; *: $p<0.05$; **: $p<0.01$; ***: $p<0.001$. See Table S1 for all statistical information.

(**C**) Comparison of the average population response of L2/3 neurons to sound playback halts while mice were running (dark gray, 4017 neurons) or sitting (light gray, 1878 neurons) in open loop session. AM mismatch duration was 1 s (gray shading).

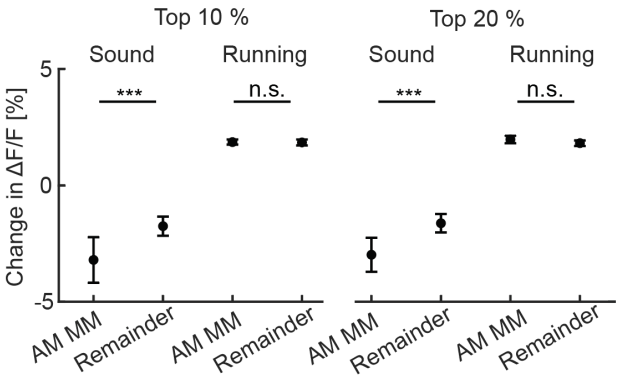


Figure S3. Opposing influence of sound and running on AM mismatch neurons. Related to Figure 2.

The same analysis presented as in **Figure 2F** but using the 10% of most AM mismatch responsive neurons (left), or the 20% of the most AM mismatch responsive neurons (right). Error bars indicate SEM. Here and elsewhere, n.s.: not significant; *: $p<0.05$; **: $p<0.01$; ***: $p<0.001$. See Table S1 for all statistical information.

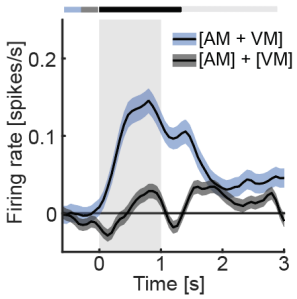


Figure S4. Non-linear combination of mismatch responses also with spike estimation. Related to Figure 4.

As in **Figure 4E**, but using an estimate of firing rate calculated using CASCADE (Rupprecht et al., 2021). Gray shading marks the duration of the mismatch stimulus.

413 **METHODS**

414 **Mice and surgery.** All animal procedures were approved by and carried out in accordance with guidelines
415 of the Veterinary Department of the Canton Basel-Stadt, Switzerland. C57BL/6 female mice (Charles
416 River), between the ages of 7 and 12 weeks were used in this study. For cranial window implantation,
417 mice were anesthetized using a mixture of fentanyl (0.05 mg/kg), medetomidine (0.5 mg/kg), and
418 midazolam (5 mg/kg). Analgesics were applied perioperatively. Lidocaine was injected subcutaneously
419 into the scalp (10 mg/kg s.c.) prior to the surgery. Mice underwent a cranial window implantation surgery
420 at an age of between 7 and 8 weeks. First, a custom-made titanium head-plate was attached to the skull
421 (right hemisphere) with dental cement (Heraeus Kulzer). Next, a 3 mm craniotomy was made over left
422 ACx (4.2 mm to 4.4 mm lateral from the midline and 2.6 mm to 2.8 mm posterior from bregma) followed
423 by 4 to 6 injections of approximately 200 nl each of the AAV vector: AAV2/1-EF1α-GCaMP6f-WPRE (10^{13-}
424 ^{14} GC/ml). A circular glass cover slip was glued (Ultragel, Pattex) in place to seal the craniotomy. Metacam
425 (5 mg/kg, s.c.) and buprenorphine (0.1 mg/kg s.c.) were injected intraperitoneally for 2 days after
426 completion of the surgery. Mice were returned to their home cage and group housed for 10 days prior to
427 the first experiments.

428 **Virtual reality environment.** All recordings were done with mice head-fixed in a virtual reality system, as
429 described previously (Leinweber et al., 2014). Mice were free to run on an air-supported polystyrene ball.
430 Three types of closed loop conditions were used for the experiments. The rotation of the spherical
431 treadmill was either coupled 1: to the sound amplitude of an 8 kHz pure tone (audiomotor coupling), while
432 the animal was locomoting in darkness, 2: to the movement in a virtual corridor (visuomotor coupling), or
433 3: to both the sound amplitude of an 8 kHz pure tone and the movement in a virtual corridor (audio-visuo-
434 motor coupling). For audiomotor coupling, we used the running speed of the mouse to control the SPL of
435 an 8 kHz pure tone presented to the mouse through a loudspeaker (see section auditory stimulation). This
436 closed loop coupling was not instantaneous but exhibited a delay of 260 ms ± 60 ms (mean ± STD). For
437 visuomotor coupling, the running speed of the mouse was coupled to the visual flow speed in the virtual
438 environment projected onto a toroidal screen surrounding the mouse using a Samsung SP-F10M projector
439 synchronized to the turnaround times of the resonant scanner of the two-photon microscope. The delay
440 in the visuomotor closed loop coupling was 90 ms ± 10 ms (mean ± STD). From the point of view of the
441 mouse, the screen covered a visual field of approximately 240 degrees horizontally and 100 degrees
442 vertically. The virtual environment presented on the screen was a corridor tunnel with walls consisting of

443 vertical sinusoidal gratings. Prior to the recording experiments, mice were habituated in darkness to the
444 setup in 1 to 2-hour long sessions for up to 5 days, until they displayed regular locomotion. Closed loop
445 sessions were followed by open loop sessions, in which rotation of the spherical treadmill was decoupled
446 from both the sound amplitude and the movement in the virtual corridor. During these open loop
447 sessions, we replayed the amplitude modulated sound or the visual flow recorded in the previous closed
448 loop session.

449 **Auditory stimulation.** Sounds were generated with a 16-bit digital-to-analog converter (PCI6738, National
450 Instruments) using custom scripts written in LabVIEW (LabVIEW 2020, National Instruments) at 160 kHz
451 sampling rate, amplified (SA1, Tucker Davis Technologies, FL, USA) and played through an MF1 speaker
452 (Tucker Davis Technologies. FL, USA) positioned 10 cm from the mouse's right ear. Stimuli were calibrated
453 with a wide-band ultrasonic acoustic sensor (Model 378C01, PCB Piezotronics, NY, USA). To study sound-
454 evoked responses, we used 4 kHz, 8 kHz, 16 kHz, and 32 kHz pure tones played at 60 dB and 75 dB SPL (1
455 s duration, at a randomized inter-stimulus interval 4 s ± 1 s, 10 repetitions, 1 ms on and off-ramp, in a
456 randomized order). For audiomotor coupling experiments, we used an 8 kHz pure tone with a sound
457 amplitude that varied between 40 dB and 75 dB SPL.

458 **Visual stimulation.** For visual stimulation, we used full-field sinusoidal drifting grating (0 degrees, 45
459 degrees, 90 degrees, 270 degrees, moving in either direction) in a pseudo-random sequence, each
460 presented for a duration of 6 s ± 2 s, with between 2 and 7 repetitions, with a randomized inter-stimulus
461 interval of 4.5 s ± 1.5 s during which a gray screen was displayed.

462 **Running onsets.** Running onsets were defined as the running speed crossing a threshold of 3 cm/s, where
463 the average speed in the previous 3 s was below 1.8 cm/s. To separate trials with AM mismatch, VM
464 mismatch, auditory stimulus and grating stimulus based on locomotion state into those running and those
465 while sitting, we used threshold of 0.3 cm/s in a 1 s window preceding the stimulus onset.

466 **Widefield calcium imaging.** To establish a reference tonotopic map of A1 and AAF (**Figure 1E**), we
467 performed widefield fluorescence imaging experiments on a custom-built microscope consisting of
468 objectives mounted face-to-face (Nikon 85 mm/f1.8 sample side, Nikon 50 mm/f1.4 sensor side), as
469 previously described (Heindorf and Keller, 2023). Blue illumination was provided by a light-emitting diode
470 (470 nm, Thorlabs) and passed through an excitation filter (SP490, Thorlabs). Green fluorescence emission
471 was filtered with a 525/50 bandpass filter. Images were acquired at a frame rate of 100 Hz on a sCMOS

472 camera (PCO edge 4.2). The raw images were cropped on-sensor, and the resulting data was saved to disk
473 with custom-written software in LabVIEW (National Instruments).

474 **Two-photon imaging.** Calcium imaging of L2/3 neurons in A1 and AAF was performed using a modified
475 Thorlabs Bergamo II microscope with a 16x, 0.8 NA objective (Nikon N16XLWD-PF), as previously
476 described (Leinweber et al., 2014). To record in left ACx, the microscope was tilted 45 degrees to the left.
477 The excitation light source was a tunable, femtosecond-pulsed laser (Insight, Spectra Physics or
478 Chameleon, Coherent) tuned to 930 nm. The laser power was adjusted to 30 mW. A 12 kHz resonance
479 scanner (Cambridge Technology) was used for line scanning, and we acquired 400 lines per frame. This
480 resulted in a frame rate of 60 Hz at a resolution of 400 × 750 pixels. We used a piezo-electric linear actuator
481 (Physik Instrumente, P-726) to record from imaging planes at four different cortical depths, separated by
482 15 µm. This reduced the effective frame rate per layer to 15 Hz. The emission light was bandpass filtered
483 using a 525/50 nm filter (Semrock), and signals were detected with a photomultiplier (Hamamatsu,
484 H7422), amplified (Femto, DHCPCA-100), digitized at 800 MHz (National Instruments, NI5772), and
485 bandpass filtered at 80 MHz with a digital Fourier-transform filter on a field-programmable gate array
486 (National Instruments, PXIe-7965). Recording locations were visually registered against the reference
487 images acquired with widefield imaging previously using blood vessels patterns.

488 **Widefield image analysis.** Off-line data processing and data analysis were done with custom-written
489 MATLAB scripts. Slow drifts in the fluorescence signal were removed using 8th percentile filtering with a
490 62.5 s moving window, similar to what was used for two-photon imaging data (Dombeck et al., 2007).
491 Activity was calculated as the $\Delta F/F_0$, where F_0 was the median fluorescence over the entire recording
492 session. For stimulus responses, we use a response window of 0.2 s to 1.2 s following stimulus onset and
493 a baseline window of -1 s to 0 s before stimulus onset. The pixels with the strongest response (top 3% -
494 5% of response distribution), were used to mark the tonotopic areas corresponding to the different
495 stimuli.

496 **Two-photon image analysis.** Calcium imaging data were processed as described previously. In brief, raw
497 images were full-frame registered to correct for lateral brain motion. Neurons were selected manually
498 based on mean and maximum fluorescence images. Average fluorescence per neuron over time was
499 corrected for slow fluorescence drift using an 8th percentile filter and a 66 s (or 1000 frames) window
500 (Dombeck et al., 2007; Keller et al., 2012; Leinweber et al., 2014) and divided by the median value over
501 the entire trace to calculate $\Delta F/F_0$. All stimulus-response curves were baseline subtracted. The baseline

502 subtraction window was -0.5 s to 0 s before stimulus onset. For quantification of responses during
503 different onset types (auditory, visual, running, mismatch), ΔF/F was averaged over the response time
504 window (0.5 s to 2.5 s after stimulus onset) and baseline subtracted (mean activity in a window preceding
505 stimulus onset, -0.5 s to 0 s). Onsets which were not preceded by at least 2 s of baseline or not followed
506 by at least 3 s of recording time, were excluded from the analysis. Sessions with less than two onsets were
507 not included in the analysis. To quantify the difference in average calcium responses as a function of time,
508 we used a hierarchical bootstrap test for every 5 frames of the calcium trace (333 ms) and marked
509 comparisons where responses were different ($p < 0.05$). Mismatch responsive neurons were selected
510 based on the absolute response strength over the response time window (0.5 s to 2.5 s). To infer spikes
511 from calcium signals (**Figure S4**), we used CASCADE (Rupprecht et al., 2021).

512 **Statistical tests.** All statistical information for the tests performed in this manuscript is provided in Table
513 S1. We used hierarchical bootstrapping (Saravanan et al., 2020) for statistical testing to account for the
514 nested structure of the data (multiple neurons from one imaging site). We first resampled the data with
515 replacement at the level of imaging sites, followed by resampling at the level of neurons. We then
516 computed the mean responses across the resampled population and repeated this process 10 000 times.
517 The probability of one group being different from the other was calculated as a fraction of bootstrap
518 sample means which violated the tested hypothesis.

519

Table S1. Statistics

All information on statistical tests used in this manuscript are shown in Table S1 below. We used hierarchical bootstrap (Saravanan et al., 2020) or a correlation coefficient for all comparisons.

Figure	Comparison	Test	N_1 (mice)	N_2 (mice)	Unit	P-value
Figure 2F	Sound response of AM mismatch responsive neurons vs that of the remainder of the population	Hierarchical bootstrap	238 (33 fields of view, 12 mice)	4517 (38 fields of view, 12 mice)	Neurons	0.0091
Figure 2F	Running onset response of AM mismatch responsive neurons vs that of the remainder of the population	Hierarchical bootstrap	238 (33 fields of view, 12 mice)	4517 (38 fields of view, 12 mice)	Neurons	0.32
Figure 2H	Correlation of the responses to AM mismatch and sound playback halt	Correlation	4755 (38 fields of view, 12 mice)	4755 (38 fields of view, 12 mice)	Neurons	$p < 0.001$ $r = 0.66$
Figure 3F	Grating response of VM mismatch responsive neurons vs that of the remainder of the population	Hierarchical bootstrap	284 (43 fields of view, 15 mice)	5404 (47 fields of view, 15 mice)	Neurons	0.23
Figure 3F	Running onset response of VM mismatch responsive neurons vs that of the remainder of the population	Hierarchical bootstrap	284 (43 fields of view, 15 mice)	5404 (47 fields of view, 15 mice)	Neurons	0.45
Figure 3H	Correlation of the responses to VM mismatch and visual flow playback halt	Correlation	5688 (47 fields of view, 15 mice)	5688 (47 fields of view, 15 mice)	Neurons	$p = 0.41$ $r = 0.01$
Figure 4F	Correlation of the responses to the concurrent [AM+VM] mismatches against the linear sum of the	Correlation	3289 (26 fields of view, 10 mice)	3289 (26 fields of view, 10 mice)	Neurons	$p < 0.001$ $r = 0.31$

	responses evoked by [AM] and [VM] mismatches presented in isolation					
Figure S2B	Running speed in AM closed loop sessions vs that in open loop	Hierarchical Bootstrap	38 sessions (12 mice)	38 sessions (12 mice)	Fields of view	0.47
Figure S3	Response to sound of the top 10% AM mismatch responsive neurons vs that of the remainder of the population	Hierarchical bootstrap	476 (36 fields of view, 12 mice)	4279 (38 fields of view, 12 mice)	Neurons	0.0004
	Response to running onsets of the top 10% AM mismatch responsive neurons vs that of the remainder of the population	Hierarchical bootstrap	476 (36 fields of view, 12 mice)	4279 (38 fields of view, 12 mice)	Neurons	0.48
	Response to sound of the top 20% AM mismatch responsive neurons vs that of the remainder of the population	Hierarchical bootstrap	951 (38 fields of view, 12 mice)	3804 (38 fields of view, 12 mice)	Neurons	0.0002
	Response to running onsets of the top 20% AM mismatch responsive neurons vs that of the remainder of the population	Hierarchical bootstrap	951 (38 fields of view s, 12 mice)	3804 (38 fields of view, 12 mice)	Neurons	0.38

527 **Key Resource Table**

REAGENT or RESOURCE	Source	Identifier
Bacterial and virus strains		
AAV2/1-EF1α-GCaMP6f-WPRE (10^{14} GC/ml)	FMI vector core	vector.fmi.ch
Chemicals, peptides, and recombinant proteins		
Fentanyl citrate	Actavis	CAS 990-73-8
Midazolam (Dormicum)	Roche	CAS 59467-96-8
Medetomidine (Domitor)	Orion Pharma	CAS 86347-14-0
Ropivacaine	Presenius Kabi	CAS 132112-35-7
Lidocaine	Bichsel	CAS 137-58-6
Buprenorphine	Reckitt Benckiser Healthcare	CAS 52485-79-7
Ophthalmic gel (Humigel)	Virbac	N/A
Flumazenil (Anexate)	Roche	CAS 78755-81-4
Atipamezole (Antisedan)	Orion Pharma	CAS 104054-27-5
N-Butyl-2-cyanoacrylate (Histoacryl)	Braun	CAS 6606-65-1
Dental cement (Paladur)	Heraeus Kulzer	CAS 9066-86-8
Meloxicam (Metacam)	Boehringer Ingelheim	CAS 71125-39-8
Deposited data		
All data and code used to generate manuscript figures	This paper	data.fmi.ch
Experimental models: Organisms/strains		
Mus musculus: C57BL/6	Charles River	N/A
Software and algorithms		
MATLAB (2021b)	The MathWorks	RRID: SCR_001622
LabVIEW	National Instruments	RRID: SCR_014325
Python	python.org	RRID: SCR_008394
Panda3D	panda3d.org	N/A

528

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532 Novartis Research Foundation (GBK), and the European Research Council (ERC) under the European
533 Union's Horizon 2020 research and innovation programme (grant agreement No 865617) (GBK).

534 **AUTHOR CONTRIBUTIONS**

535 MS designed and performed the experiments and analyzed the data. All authors wrote the manuscript.

536 **DECLARATION OF INTERESTS**

537 The authors declare no competing financial interests.

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