Title: Where are multisensory signals combined for perceptual decision-making?

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Abstract

Multisensory integration is observed in many sub-cortical and cortical locations including primary and non-primary sensory cortex, and higher cortical areas including frontal and parietal cortex. During unisensory perceptual tasks many of these same brain areas show neural signatures associated with decision-making. It is unclear whether multisensory representations in sensory cortex directly inform decision-making in a multisensory task, or if cross-modal signals are only combined after the accumulation of unisensory evidence at a final decision-making stage in higher cortical areas. Manipulations of neuronal activity are required to establish causal roles for given brain regions in multisensory perceptual decision-making, and so far indicate that distributed networks underlie multisensory decision-making. Understanding multisensory integration requires synthesis of small-scale pathway specific and large-scale network level manipulations.

Highlights

- Multisensory integration is observed in sensory cortices and higher cortical areas
- Multisensory information could be integrated early and/or late in decision-making
- Manipulation of neural activity allows causal relationships to be established
- Causal tests indicate distributed networks underlie multisensory decision-making

Introduction

Multisensory integration is evident in many behaviours and occurs at multiple locations in the brain [1]. Perceptual decision-making is the process by which sensory evidence is evaluated in order to make a decision and guide behaviour. Different sensory systems can provide independent estimates of a real-world source that are often complementary; for example, visual signals typically provide more precise spatial information, whereas auditory signals offer superior temporal resolution [2]. Integrating signals across sensory modalities can therefore reduce the inherent uncertainty within any sensory estimate and so improve performance in perceptual decision-making tasks. In the mammalian brain, the neural processes underlying decision-making [3,4] and multisensory integration [5-7] have become increasingly well understood but remain largely independent lines of investigation. In particular, it remains an open question at what point(s) in the decision-making process information is combined across modalities. Here we address the question of how and where across-sensory information is combined for perceptual decision-making, and highlight the importance of manipulating neural activity in order to determine causal roles of early and late multisensory integration in decision-making.

Multisensory integration in perceptual decision-making

Perceptual decision-making is traditionally viewed as a serial, hierarchical process moving from the encoding of sensory information, to the accumulation of sensory evidence, through the calculation of decision variables and application of decision rules, and finally to production of a motor response [3,4]. Encoding of (uni)sensory evidence emerges in the sensory cortices of the mammalian brain [8 ,9-11] while evidence accumulation and decision formation are associated with pre-motor, parietal, and frontal areas [12-14].

The neural basis of perceptual decision-making has mostly been studied in unisensory paradigms (see Refs [15,16] for exceptions), but multisensory decision-making is likely to follow similar principles. However, a key question is at what point(s) evidence across sensory modalities is combined, and whether this occurs before or during decision-making. Two theoretical extremes could be hypothesized (Figure 1): In one case, multisensory integration occurs at the same time as decision-making, with unisensory evidence accumulated in independent channels within sensory cortices and unisensory decision variables subsequently integrated to make a multisensory decision in higher order areas (Figure 1a). Alternatively, multisensory integration beginning in the sensory cortex contributes to the accumulation of sensory evidence. Decision-making in higher order areas is then based on an already multisensory representation (Figure 1b). A third, and perhaps most likely option, is that multisensory decision making is distributed and incorporates elements of both models.

In support of the early integration hypothesis, there is substantial physiological [e.g. 17,18-20] and anatomical [21,e.g. 22,23-25] evidence for multisensory interactions in primary and non-primary sensory cortices. Although the functional role of such interactions in shaping perception and behaviour is unknown, early cross-modal integration offers the possibility that multisensory representations are fed into later decision-making processes. Only one study has, to our knowledge, directly addressed whether cross-modal signals in primary sensory areas feed into perceptual decision-making: Lemus *et al.,* [16] recorded from primary auditory and somatosensory cortices during the performance of a rate comparison task in which subjects were required to compare stimuli that were presented in two intervals separated by a short delay. The stimuli were auditory or somatosensory, and could be unisensory, mixed (i.e. one modality in each interval), or multisensory (both modalities in both intervals). The authors found no evidence for cross-sensory neural responses that were informative about the comparison or the monkey's decision. However, the monkeys showed no behavioural benefit in the multisensory relative to mixed or unisensory conditions, complicating the interpretation of this study as it is unclear whether the animals actually integrated stimuli across modalities.

A number of studies have correlated multisensory integration in sensory cortex with behavioural outcomes [18,26-28]. It therefore seems possible for early multisensory integration in sensory cortex to inform multisensory decision-making by shaping neuronal signals in sensory specific cortex. Both the prevalence of multisensory interactions, and the likelihood of observing a relationship between neuronal firing and behavioural choice in a sensory discrimination task, increase from primary to non-primary sensory cortex in visual [29-31], somatosensory [32], and auditory cortices [9,33,34]. Thus, many of the same areas in which multisensory integration is observed have also been implicated in the accumulation of sensory evidence. In at least one case, evidence for multisensory cue weighting has been observed in higher sensory cortex: in the case of integrating visual and vestibular cues during heading discrimination, neural activity in macaque dorsal medial superior temporal area (dMST) predicts behavioural cue integration [28,35,36].

In contrast to the evidence above suggesting that multisensory signals are integrated in sensory cortex, recent psychophysical investigations support the idea of late integration where unisensory decision estimates are combined. For example Churchland and colleagues [15,37] demonstrated improved accuracy in multisensory conditions of an audio-visual rate categorisation task. Subjects were required to categorise stimuli according to a learned boundary as either “fast” or “slow”, depending on the number of stimulus “events” (20 ms tones or flashes) contained in each stream. Stimulus rate could not be determined from inter-event interval, forcing subjects to integrate information over time. Performance improved when subjects were presented simultaneously with both auditory and visual streams, compared to either alone and subjects integrated multisensory information according to its reliability [37]. This multisensory performance benefit persisted in an asynchronous condition where visual and auditory stimuli were presented with the same number of events (indicating the same choice), but distributed differently within each stream. Since the two asynchronous streams were less likely to be integrated into a single perceptual object, the authors concluded that unisensory decisions were formed prior to their integration to reach a multisensory decision.

Neurophysiology and neuroimaging results also support later cross-modal integration in areas beyond sensory cortex, traditionally associated with decision-making. Parietal and frontal areas process multisensory stimuli in a manner indicative of a role in multisensory decision-making: In humans, the inferior frontal sulcus displays activity consistent with a role in the accumulation of evidence [38] while higher order parietal areas (specifically the anterior intraparietal sulcus) combine sensory signals according to their reliability as predicted by Bayesian causal inference [39]. The work of Rohe and Noppeney demonstrates that distinct computational principles underlie multisensory integration in parietal and sensory cortices: Parietal cortex integrated auditory and visual information by weighting modality information depending on task (top-down) relevance and (bottom-up) reliability, whereas multisensory integration in sensory cortices was mediated by temporal and spatial coherence between sensory stimuli in different modalities. This study indicates that multisensory information is brought together in higher cortical areas during decision-making, consistent with the late integration hypothesis. Nevertheless, this does not necessarily contradict the early integration model; if multisensory information is integrated into areas classically considered to be unisensory, it seems likely that this earlier integration will also influence the downstream representations in decision-making areas.

Causality in distributed networks

To fully understand the relationship between multisensory integration and decision-making, it is necessary to establish the perceptual relevance of integration at different levels. For example, it is possible that neurons in sensory areas integrating cross-modal stimuli make no contribution to decision-making. This issue cannot be addressed with behavioural neurophysiology or neuroimaging alone and requires neural manipulation to establish the causal effects of perturbing multisensory integration [7]. So far, causal contributions of both sensory and higher order areas to multisensory integration have been shown in humans [40-42] and other animals [26,43-45]. However few studies have tested the role of cortical regions in multisensory perceptual decision-making tasks. This is critical, as in unisensory perceptual decision-making tasks inactivation studies have demonstrated regions such as posterior parietal cortex (PPC), in which neuronal responses appear to reflect the accumulation of sensory evidence, are unnecessary for auditory decision-making [46]. Similarly, PPC inactivation does not disrupt auditory-visual integration at the behavioural level [47] despite PPC neurons encoding both auditory and visual signals and inactivation impairing (unisensory) visual decision-making. Such findings mirror reports in dMST where neurons integrate visual and vestibular signals during discrimination of the animal's movement heading. Inactivation of dMST most profoundly affects visual discrimination thresholds in this task, with much weaker effects on vestibular thresholds [44]. Similarly, microstimulation of dMST affects visual, but not vestibular, discrimination performance [44]. Together these findings indicate that while neurons in regions such as dMST and PPC may integrate across modalities, the contribution of such regions to multisensory decision-making may not be straightforward[48]. The emerging picture from correlative and causal studies of decision-making and multisensory integration instead suggests that neither process is restricted to particular areas of the brain. As such both early and late multisensory integration are likely to contribute to decision-making as both processes engage distributed cortical (and subcortical) networks.

If large-scale distributed networks underlie multisensory decision-making, this presents additional challenges when determining the contributions of cortical areas to perception and behaviour as techniques that manipulate neural activity tend to trade between spatial range and resolution. For example, techniques such as transcranial magnetic stimulation (TMS) and direct transcranial current stimulation (tDCS) affect large volumes of cortex, potentially altering both multisensory integration and decision-making. More local techniques such as pharmacological inactivation, optogenetics, or cortical cooling have better spatial resolution, but act on a much smaller scale. An ideal solution to this range/resolution trade-off would be to exploit the spatial specificity of invasive methods while maintaining the ability to affect targets anywhere in the brain, perhaps by simultaneously locally manipulating different network components in parallel: Simultaneous recordings from multiple (six) cortical regions have revealed the flow of sensory and task information within frontoparietal networks during complex decision-making at the cellular level [29]. Similar optogenetic or chemogenetic control of several brain regions could be achieved through multiple virus injections; in this line of experiment the chemogenetic approach [49] is particularly attractive as a single ligand could affect multiple brain areas, without the need for chronically implanted optic fibers. If multiple chemogenetically encoded proteins were expressed at distinct sites, combinations of ligands (still provided in a single injection) could be used to dissect circuit function. The behavioural effects of inactivation can be used to determine what role an area plays in a multisensory decision making task: for example, in an area that processes inputs from multiple senses without integrating cross-sensory information inactivation should impair performance in both (uni)sensory modalities as well as in the multisensory condition. In contrast, inactivation of an area that integrates information across the senses should lead to a loss of multisensory enhancement with performance being reduced to the level of the best unisensory condition and performance preserved in unisensory conditions. Given the apparently distributed nature of multisensory decision-making it seems likely that inactivating any one area may result in compensation from other areas: careful analysis of reaction times and response trajectories may help detect subtle changes in performance elicited by silencing a brain region that is ordinarily involved in behavior.

Functional connectivity

Network connectivity also complicates investigations of causal links between brain areas during multisensory integration and decision-making. The standard experimental design to test functional connectivity is to manipulate the activity in one region and observe any resulting effects in another. However in distributed networks, downstream effects may be realized through direct connections between regions, or via indirect pathways involving intermediary regions (Figure 2a). These mechanisms cannot be distinguished by broad/non-specific techniques that affect neurons regardless of connectivity (e.g. cooling, pharmacological inactivation, or micro-stimulation) (Figure 2b). In multisensory systems, this is particularly problematic as sensory pathways interconnect at cortical and subcortical levels [22-25,50,51]. For example, visual information in non-primary auditory cortex may originate from direct connections with visual cortex, from earlier interactions between primary auditory and visual cortices (or multisensory thalamus) that are subsequently inherited through the ascending auditory system, or from top-down feedback from higher brain regions. Resolving the functional contribution of direct connections between cortical areas requires *pathway specific* manipulation of neural activity in which neural signals arriving in a region of interest are perturbed while the signal source (i.e. neurons in an upstream region) is left unaffected.

Pathway specific manipulation is possible through recent advances in optogenetic terminal field excitation/inhibition, in which a target region is transfected with a viral vector inducing the expression of an opsin both in the cell body and axons [52,53]. Illuminating axon terminals in the downstream region of interest allows control of the direct pathway while leaving unaffected axon terminals in the same area that arrive from other intermediary brain regions (Figure 2c). Such techniques can advance models that describe the specific role of network connections (Town *et al.*, unpublished data) and offer significant opportunities to enhance our understanding of multisensory interactions in decision-making circuits. Pathway specific investigation via terminal field stimulation/silencing also offers the ability to maintain normal unisensory processing while only perturbing cross-modal connections: for example, one could perturb auditory-visual integration in auditory cortex by expressing a viral vector in visual cortex and manipulating neural activity through terminal field stimulation/silencing in auditory cortex. Both unisensory auditory and visual processing would be maintained, but visual information would no longer be integrated into auditory cortex via the inactivated pathway. Furthermore, the temporal resolution with which opsins can modulate neural activity enables pathway specific manipulation within restricted time windows during behaviour [14,46]. Temporal control of circuit interactions will be critical in determining whether early or late integration contributes to decision-making.

Towards a synthesis

Early multisensory integration in sensory cortex offers the potential for decision-making based on multisensory representations. There is also substantial evidence for integration of cross-modal signals later in the decision-making process. Whether correlates of multisensory evidence accumulation and decision-making are observed in sensory cortex as well as, or instead of, in higher areas may depend on the nature of the task and on whether multisensory signals are perceived as originating from a single perceptual object [5].

Understanding the neural basis of multisensory perceptual decision-making requires solutions to conflicting demands: The need to manipulate broad swathes of distributed networks in order to reveal the causal involvement of brain regions in crossmodal behaviour, and the need to use pathway specific, temporally precise manipulations to dissect the roles of identified circuit connections. This divide between connectivity, network function and behaviour has been bridged in smaller, more tractable brains [54] that may inform circuit models of multisensory integration and decision making in mammalian systems, in which progress at each level (pathway, network and behavior) is likely to proceed along parallel lines in the immediate future.

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Figures

Figure 1 Integration of multisensory signals for decision-making

(A) Late multisensory integration occurring at the decision-making stage in higher cortices. In this case, unisensory processing and evidence accumulation occur separately for each modality and combined after unisensory decision are made.

(B) Earlier multisensory integration in sensory cortex may inform evidence accumulation and decision-making before individual modality decisions are made.

Figure 2 Resolving functional connectivity with optogenetics

(**A**) Circuit diagram illustrating direct and indirect pathways between two brain regions (A and B). (**B**) Somatic perturbations such as pharmacological inactivation, micro-stimulation, lesions or cooling affect all neurons in, and pathways from the manipulated region regardless of connectivity. (**C**) Terminal field perturbation in which neurons in the first brain region express an opsin introduced by viral vector (e.g. adeno-associate virus; AAV). Axon terminals from the same neurons projecting to the target of interest are then manipulated by light delivery via optic fibre. Terminals from intermediary areas do not express the opsin and so remain unaffected.

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Annotated references:

***Erlich et al., 2015** inactivated two areas thought to be associated with the accumulation of evidence in a decision making task (FOF and PPC) and demonstrated that PPC inactivation did not influence decision-making behaviour and that FOF inactivation was more consistent with impairment of an output pathway than with the accumulator itself.

****Hanks et al., 2015** combine electrophysiological recordings during behaviour with computational methods to determine that activity in FOF is most consistent with representing a categorical decision. Consistent with this, optogenetic inactivation silencing of FO only influenced behaviour when targeted to the end of the stimulus.

Rohe and Noppeney 2016 Demonstrate that spatial disparity determines the likelihood of multisensory integration in sensory cortex while only in parietal cortex were auditory and visual signals weighted by their reliability and task relevance.

***Tsunada et al., 2015** Demonstrates that two tonotopic belt areas (AL and ML) of auditory cortex show similar stimulus tuning and that significant choice probabilities are observed in both fields but only in AL did microstimulation systematically bias behavioural judgments.

****Siegal et al., 2015** simultaneously record from six areas of visual and frontoparietal cortices during flexible decision-making to reveal network dynamics of choice activity where signals first emerge in lateral prefrontal and intraparietal cortex and then subsequently processed in FOF and also fed back to visual areas MT, VT and inferior temporal cortex.

***Oyhama et al., 2015** combine behavioral and physiological studies with large-scale electrode microscopy to map at the single cell level, a distributed network of identified neurons underlying multisensory integration during escape locomotion of *Drosophila* larvae.

****Raposo et al., 2014** demonstrated that individual neurons on the PPC are not members of set processing categories or receptive fields, and dynamic networks containing random neurons are formed to handle the evolving demands at subsequent stages of decision making.

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