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

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35 Abstract

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37 Multisensory integration is observed in many sub-cortical and cortical locations including primary
38 and non-primary sensory cortex, and higher cortical areas including frontal and parietal cortex.

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

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49 Highlights

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

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56 Introduction

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

71

72 Multisensory integration in perceptual decision-making

73 Perceptual decision-making is traditionally viewed as a serial, hierarchical process moving from the
74 encoding of sensory information, to the accumulation of sensory evidence, through the calculation
75 of decision variables and application of decision rules, and finally to production of a motor response
76 [3,4]. Encoding of (uni)sensory evidence emerges in the sensory cortices of the mammalian brain [8
77 ,9-11] while evidence accumulation and decision formation are associated with pre-motor, parietal,
78 and frontal areas [12-14].

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

91 In support of the early integration hypothesis, there is substantial physiological [e.g. 17,18-
92 20] and anatomical [21,e.g. 22,23-25] evidence for multisensory interactions in primary and non-
93 primary sensory cortices. Although the functional role of such interactions in shaping perception and
94 behaviour is unknown, early cross-modal integration offers the possibility that multisensory
95 representations are fed into later decision-making processes. Only one study has, to our knowledge,
96 directly addressed whether cross-modal signals in primary sensory areas feed into perceptual
97 decision-making: Lemus *et al.*, [16] recorded from primary auditory and somatosensory cortices
98 during the performance of a rate comparison task in which subjects were required to compare
99 stimuli that were presented in two intervals separated by a short delay. The stimuli were auditory or
100 somatosensory, and could be unisensory, mixed (i.e. one modality in each interval), or multisensory
101 (both modalities in both intervals). The authors found no evidence for cross-sensory neural
102 responses that were informative about the comparison or the monkey's decision. However, the
103 monkeys showed no behavioural benefit in the multisensory relative to mixed or unisensory

104 conditions, complicating the interpretation of this study as it is unclear whether the animals actually
105 integrated stimuli across modalities.

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

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

129 stream. Since the two asynchronous streams were less likely to be integrated into a single
130 perceptual object, the authors concluded that unisensory decisions were formed prior to their
131 integration to reach a multisensory decision.

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

148

149 [Causality in distributed networks](#)

150 To fully understand the relationship between multisensory integration and decision-making,
151 it is necessary to establish the perceptual relevance of integration at different levels. For example, it
152 is possible that neurons in sensory areas integrating cross-modal stimuli make no contribution to
153 decision-making. This issue cannot be addressed with behavioural neurophysiology or neuroimaging

154 alone and requires neural manipulation to establish the causal effects of perturbing multisensory
155 integration [7]. So far, causal contributions of both sensory and higher order areas to multisensory
156 integration have been shown in humans [40-42] and other animals [26,43-45]. However few studies
157 have tested the role of cortical regions in multisensory perceptual decision-making tasks. This is
158 critical, as in unisensory perceptual decision-making tasks inactivation studies have demonstrated
159 regions such as posterior parietal cortex (PPC), in which neuronal responses appear to reflect the
160 accumulation of sensory evidence, are unnecessary for auditory decision-making [46]. Similarly, PPC
161 inactivation does not disrupt auditory-visual integration at the behavioural level [47] despite PPC
162 neurons encoding both auditory and visual signals and inactivation impairing (unisensory) visual
163 decision-making. Such findings mirror reports in dMST where neurons integrate visual and vestibular
164 signals during discrimination of the animal's movement heading. Inactivation of dMST most
165 profoundly affects visual discrimination thresholds in this task, with much weaker effects on
166 vestibular thresholds [44]. Similarly, microstimulation of dMST affects visual, but not vestibular,
167 discrimination performance [44]. Together these findings indicate that while neurons in regions such
168 as dMST and PPC may integrate across modalities, the contribution of such regions to multisensory
169 decision-making may not be straightforward[48]. The emerging picture from correlative and causal
170 studies of decision-making and multisensory integration instead suggests that neither process is
171 restricted to particular areas of the brain. As such both early and late multisensory integration are
172 likely to contribute to decision-making as both processes engage distributed cortical (and subcortical)
173 networks.

174 If large-scale distributed networks underlie multisensory decision-making, this presents
175 additional challenges when determining the contributions of cortical areas to perception and
176 behaviour as techniques that manipulate neural activity tend to trade between spatial range and
177 resolution. For example, techniques such as transcranial magnetic stimulation (TMS) and direct
178 transcranial current stimulation (tDCS) affect large volumes of cortex, potentially altering both
179 multisensory integration and decision-making. More local techniques such as pharmacological

180 inactivation, optogenetics, or cortical cooling have better spatial resolution, but act on a much
181 smaller scale. An ideal solution to this range/resolution trade-off would be to exploit the spatial
182 specificity of invasive methods while maintaining the ability to affect targets anywhere in the brain,
183 perhaps by simultaneously locally manipulating different network components in parallel:
184 Simultaneous recordings from multiple (six) cortical regions have revealed the flow of sensory and
185 task information within frontoparietal networks during complex decision-making at the cellular level
186 [29]. Similar optogenetic or chemogenetic control of several brain regions could be achieved through
187 multiple virus injections; in this line of experiment the chemogenetic approach [49] is particularly
188 attractive as a single ligand could affect multiple brain areas, without the need for chronically
189 implanted optic fibers. If multiple chemogenetically encoded proteins were expressed at distinct
190 sites, combinations of ligands (still provided in a single injection) could be used to dissect circuit
191 function. The behavioural effects of inactivation can be used to determine what role an area plays in
192 a multisensory decision making task: for example, in an area that processes inputs from multiple
193 senses without integrating cross-sensory information inactivation should impair performance in both
194 (uni)sensory modalities as well as in the multisensory condition. In contrast, inactivation of an area
195 that integrates information across the senses should lead to a loss of multisensory enhancement
196 with performance being reduced to the level of the best unisensory condition and performance
197 preserved in unisensory conditions. Given the apparently distributed nature of multisensory
198 decision-making it seems likely that inactivating any one area may result in compensation from other
199 areas: careful analysis of reaction times and response trajectories may help detect subtle changes in
200 performance elicited by silencing a brain region that is ordinarily involved in behavior.

201

202 [Functional connectivity](#)

203 Network connectivity also complicates investigations of causal links between brain areas
204 during multisensory integration and decision-making. The standard experimental design to test

205 functional connectivity is to manipulate the activity in one region and observe any resulting effects
206 in another. However in distributed networks, downstream effects may be realized through direct
207 connections between regions, or via indirect pathways involving intermediary regions (Figure 2a).
208 These mechanisms cannot be distinguished by broad/non-specific techniques that affect neurons
209 regardless of connectivity (e.g. cooling, pharmacological inactivation, or micro-stimulation) (Figure
210 2b). In multisensory systems, this is particularly problematic as sensory pathways interconnect at
211 cortical and subcortical levels [22-25,50,51]. For example, visual information in non-primary auditory
212 cortex may originate from direct connections with visual cortex, from earlier interactions between
213 primary auditory and visual cortices (or multisensory thalamus) that are subsequently inherited
214 through the ascending auditory system, or from top-down feedback from higher brain regions.
215 Resolving the functional contribution of direct connections between cortical areas requires *pathway*
216 *specific* manipulation of neural activity in which neural signals arriving in a region of interest are
217 perturbed while the signal source (i.e. neurons in an upstream region) is left unaffected.

218 Pathway specific manipulation is possible through recent advances in optogenetic terminal
219 field excitation/inhibition, in which a target region is transfected with a viral vector inducing the
220 expression of an opsin both in the cell body and axons [52,53]. Illuminating axon terminals in the
221 downstream region of interest allows control of the direct pathway while leaving unaffected axon
222 terminals in the same area that arrive from other intermediary brain regions (Figure 2c). Such
223 techniques can advance models that describe the specific role of network connections (Town *et al.*,
224 unpublished data) and offer significant opportunities to enhance our understanding of multisensory
225 interactions in decision-making circuits. Pathway specific investigation via terminal field
226 stimulation/silencing also offers the ability to maintain normal unisensory processing while only
227 perturbing cross-modal connections: for example, one could perturb auditory-visual integration in
228 auditory cortex by expressing a viral vector in visual cortex and manipulating neural activity through
229 terminal field stimulation/silencing in auditory cortex. Both unisensory auditory and visual
230 processing would be maintained, but visual information would no longer be integrated into auditory

231 cortex via the inactivated pathway. Furthermore, the temporal resolution with which opsins can
232 modulate neural activity enables pathway specific manipulation within restricted time windows
233 during behaviour [14,46]. Temporal control of circuit interactions will be critical in determining
234 whether early or late integration contributes to decision-making.

235

236 [Towards a synthesis](#)

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

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

251

252 [Acknowledgments](#)

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254 Frontiers Science Program grant (RGY0068).

255 **Figures**

256 **Figure 1 Integration of multisensory signals for decision-making**

- 257 (A) Late multisensory integration occurring at the decision-making stage in higher cortices. In
258 this case, unisensory processing and evidence accumulation occur separately for each
259 modality and combined after unisensory decisions are made.
260 (B) Earlier multisensory integration in sensory cortex may inform evidence accumulation and
261 decision-making before individual modality decisions are made.

262

263 **Figure 2 Resolving functional connectivity with optogenetics**

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

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274 [References](#)

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278 **Annotated references:**

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

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

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

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

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

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

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

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427