Multisensory integration: current issues from the perspective of the single neuron

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Abstract | For thousands of years science philosophers have been impressed by how effectively the senses work together to enhance the salience of biologically meaningful events. However, they really had no idea how this was accomplished. Recent insights into the underlying physiological mechanisms reveal that, in at least one circuit, this ability depends on an intimate dialogue among neurons at multiple levels of the neuraxis; this dialogue cannot take place until long after birth and might require a specific kind of experience. Understanding the acquisition and usage of multisensory integration in the midbrain and cerebral cortex of mammals has been aided by a multiplicity of approaches. Here we examine some of the fundamental advances that have been made and some of the challenging questions that remain.

Multisensory integration
The neural processes that are involved in synthesizing information from cross-modal stimuli. It should not be confused with the particular underlying neural computation that determines multisensory integration's relative magnitude (superadditive, additive or subadditive).

Cross-modal stimuli
Stimuli from two or more sensory modalities or an event providing such stimuli. This term should not be confused with the term 'multisensory'.

Multisensory enhancement
A situation in which the response to the cross-modal stimulus is greater than the response to the most effective of its component stimuli.

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Encoding, decoding and interpreting information about biologically significant events are among the brain's most important functions, and collectively they require a good deal of neural circuitry. These functions have been powerful driving forces in evolution and have led to the development of an array of specialized sensory organs, each of which is linked to multiple specialized brain regions.

There are obvious advantages associated with having multiple senses: each sense is of optimal usefulness in a different circumstance, and collectively they increase the likelihood of detecting and identifying events or objects of interest. However, these advantages pale in comparison with those afforded by the ability to combine sources of information. In this case the integrated product reveals more about the nature of the external event and does so faster and better than would be predicted from the sum of its individual contributors. It might be surprising to find that this is not a new evolutionary strategy: our earliest single-celled progenitor is thought to have been endowed with multiple 'senses' (that is, receptors for different environmental stimuli) and the ability to use them synergistically[1].

It is this synergy, or interaction, among the senses, and the fusion of their information content, that is described by the phrase 'multisensory integration'. Multisensory integration is most commonly assessed by considering the effectiveness of a cross-modal stimulus combination, in relation to that of its component stimuli, for evoking some type of response from the organism. For example,

the likelihood or magnitude of a response to an event that has both visual and auditory components is compared with that for the visual and the auditory stimuli alone. At the level of the single neuron, multisensory integration is defined operationally as: a statistically significant difference between the number of impulses evoked by a cross-modal combination of stimuli and the number evoked by the most effective of these stimuli individually[2].

Multisensory integration can therefore result in either enhancement or depression of a neuron's response. In principle, the magnitude of multisensory integration is a measure of the relative physiological salience of an event[3]. If one imagines that sensory stimuli compete for attention and for access to the motor machinery that generates reactions to them, then the potential consequence of multisensory enhancement (or multisensory depression) is an increased (or decreased, for depression) likelihood of detecting and/or initiating a response to the source of the signal (FIG. 1, also see REFS 4–6 for reviews). The extent to which multisensory integration aids the detection of an event has a direct, positive effect on the speed with which a response can be generated[7–11]. The magnitude of multisensory integration can vary widely for different neurons and even for the same neuron encountering different cross-modal stimulus combinations. For multisensory enhancement (the form of interaction on which we will mainly focus), differences in magnitude reflect different underlying computations. The largest enhancements are due to superadditive combinations of cross-modal influences and the smallest are due to subadditive
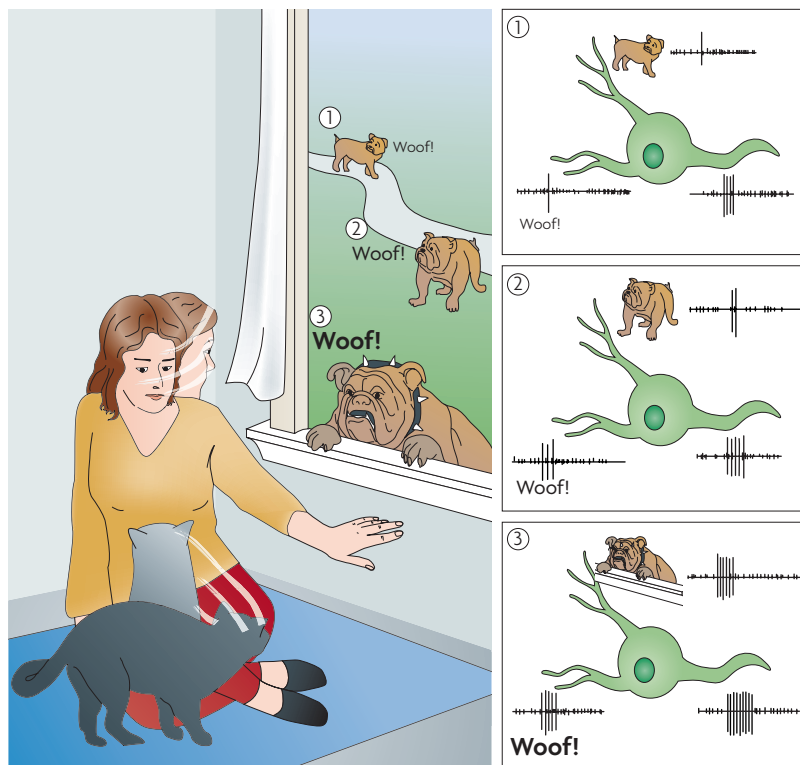
Figure 1 | **Multisensory integration aids detection and speeds responses.** A woman and cat detect the approach of a dog, based on sight and sound. When these cues are weak (when the dog is far away), the neural computation involved in their integration is superadditive, such that the response not only exceeds the most vigorous component response, but also exceeds their sum (top). As the dog gets closer, the cues become more effective, unisensory component responses become more vigorous, and integrated responses become proportionately smaller. The computation now becomes additive (middle) and then subadditive (bottom). Although both the additive and the subadditive computations also produce responses that exceed the most vigorous component response (that is, they all exhibit multisensory integration), their enhancements are proportionately less than the one shown at the top. All enhancements increase the probability of orientation, but the benefits of multisensory integration are proportionately greatest when cross-modal cues are weakest. Figure modified, with permission, from REF. 3 © (2007) Lippincott Williams & Wilkins.

Multisensory depression
A situation in which the response to the cross-modal stimulus is less than the response to the most effective of its component stimuli.

Qualia
The qualities of sensation such as the subjective impression that a sensation gives.

Multisensory neuron
A neuron that responds to, or is influenced by, stimuli from more than one sensory modality.

Receptive field
The area of sensory space in which presentation of a stimulus leads to the response of a particular neuron.

combinations. Along with changes in sensory-response magnitude, multisensory integration can shorten the interval between sensory encoding and motor-command formation[7], and it can speed sensory processing itself by enhancing the initial subthreshold portion of a response such that the multisensory response has a significantly shorter latency than either of the component unisensory responses[12].

In addition to altering the salience of cross-modal events, multisensory integration involves creating unitary perceptual experiences. Taste, for example, emerges from the synthesis of gustatory, olfactory, tactile and sometimes visual information. This raises some nontrivial issues: integrating information from different senses must take into account not only the inherent complexities of information processing in each individual modality, but also the fact that each modality has its own unique subjective impressions or 'qualia' (for example, the perception of hue is specific to the visual system, whereas tickle and itch are specific to the somatosensory

system) that must not be disrupted by the integrative process. Although we still do not fully understand how this is accomplished, we have learned some of the strategies that the nervous system uses to integrate (or 'bind') cues from different senses so that they produce a unitary experience. Often this is accomplished by weighting the various cues based on how much information they are likely to provide about a given event[13–15]. In this context it is important to recognize that information in any given sensory category is always dealt with against a background of inputs from many senses, thereby complicating the task of deciding which of them are appropriate for binding. It is interesting to note that we are largely unaware of these processes except when small temporal and/or spatial discrepancies disrupt the tight links between cross-modal cues that are naturally associated; this often results in a vivid illusion (BOX 1).

The benefits of multisensory integration for orienting behaviour have received a good deal of attention and provided many insights into the neural mechanisms that underlie the integration of sensory information (BOX 2). These insights have been derived from physiological studies of individual multisensory neurons in a number of species and brain regions, particularly in the midbrain and cerebral cortex of cats and monkeys. By contrast, we know much less about the physiological processes that underlie higher-order multisensory processes, such as perceptual binding. These inquiries are in their nascent stages. Thus, this Review focuses heavily on the insights obtained from physiological studies in single neurons, and examines how that information has influenced our thinking about the impact of multisensory integration on behaviour and perception. We begin by briefly reviewing what is known about the properties of multisensory neurons in the midbrain and the role of these neurons in orienting behaviour. We then consider a host of current issues relating to multisensory integration in the cerebral cortex of the cat, the monkey and the human brain. In doing so, we move beyond simple orienting behaviour to explore the neural bases of some higher-order multisensory phenomena.

Multisensory neurons in the superior colliculus
Multisensory neurons respond to stimuli from more than a single sense. Although they are present at all levels in the brain and in all mammals, they are particularly abundant in the superior colliculus (SC) of cats, making it a rich source of information about their properties. This midbrain structure controls changes in orientation (for instance, gaze shifts) in response to stimuli in the visual space on the opposite side of the head to the SC under study. Its visual, auditory and somatosensory inputs are derived from ascending sensory pathways and descending projections from the cortex, which converge in various combinations on SC neurons.

The principles of multisensory integration in SC neurons. The spatial principle is an issue of particular importance for the orienting role of the SC. Each multisensory neuron has multiple excitatory receptive fields, one for each modality to which it responds. These receptive fields are

Box 1 | **Cross-modal illusions**

There are many examples of cross-modal illusions, but two of the best-known ones involve alterations in either the meaning or the apparent location of an event. A very popular example of the first, which is also a favourite of speech professionals, is called the McGurk Effect[88]. Ordinarily, watching a speaker's face helps us understand what is being said because integrating the sight (lip movements) and sound of speech enhances the brain activity that underlies speech perception[60,89,90]. However, if slightly mismatched cues are paired (such as the sound for 'bows' with the lip movements for 'goes'), the resulting synthesis yields an entirely different product ('doze' or 'those').

The best-known example of the second type of illusion is the Ventriloquism Effect[91], in which the speaker's lips appear to 'capture' a sound and translocate it. This is also what we experience when watching a movie. Each character's voice is properly located on the screen, regardless of the movement of the character, but all sounds actually come from the identical static location (the audio speakers). Other such illusions include the 'parchment skin' illusion, whereby the texture of the skin appears to change when the subject rubs their fingers together in synchrony with a grating sound heard through earphones[92]; the 'flash' illusion, whereby a single light-flash associated with two beeps is perceived as a double flash[93]; and the 'oculogravic' illusion, whereby visual judgments are altered by vestibular cues[94].

in spatial register with one another (for example, the two receptive fields of a visual–auditory neuron overlap in space), so that the location of an event, rather than the modality it activates, is of greatest importance in determining whether the neuron is activated (FIG. 2). These two stimulus modalities will be defined as originating from the same source location as long as they are within the space that is registered by their overlapping receptive fields; they do not need to originate from an identical point source in space[16]. If the stimuli are derived from spatially disparate locations, such that one stimulus falls within and the other outside the neuron's receptive field, there will be either no enhancement or response depression[17–19]. The response depression occurs when the second stimulus lies within an inhibitory region that borders the excitatory receptive fields of some SC neurons, and can be powerful enough to suppress the excitation evoked by the other stimulus.

The spatial principle of multisensory integration is remarkably robust and is evident in a host of perceptual situations in which the location of the event is crucial. However, the need to maintain receptive-field register and the ability to move each sense organ independently seem to be incompatible. A solution adopted by the SC is to link the various modality-specific receptive fields to the position of the eyes. For example, moving the eyes leftward produces compensatory shifts in both auditory[20–22] and somatosensory receptive fields[23]. Such compensation for eye movements seems to create a common oculocentric coordinate frame, ensuring that the individual stimulus components of a cross-modal event interact to produce a single, coherent locus of activity within the SC sensory–motor map. The issues of common coordinate frames and the implications of incomplete compensatory receptive-field shifts for multisensory integration are discussed below.

If they are to be integrated, different sensory stimuli must also be linked in time[24,25]. In general, these stimuli can reach the nervous system within a window of time that is comparatively long, sometimes lasting several hundred milliseconds. This enables integration

to take place despite the different response latencies, conduction speeds and onsets of visual, auditory and somatosensory stimuli. The magnitude of the integrated response is sensitive to the temporal overlap of the responses that are initiated by each sensory input and is usually maximal when the peak periods of activity coincide.

Multisensory enhancement is typically inversely related to the effectiveness of the individual cues that are being combined[26]. This principle of inverse effectiveness makes intuitive sense. Individual cues that are highly salient will be easily detected and localized. Thus, their combination has a proportionately modest effect on neural activity and behavioural performance. By contrast, weak cues evoke comparatively few neural impulses and their responses are therefore subject to substantial enhancement when stimuli are combined. In these cases the multisensory response can exceed the arithmetic sum of their individual responses[3,26–29] and can have a significant positive effect on behavioural performance by increasing the speed and likelihood of detecting and locating an event[7–11,30–32].

Descending excitatory inputs from a specific region of the association cortex are essential for multisensory integration in SC neurons. These inputs mainly come from the anterior ectosylvian sulcus (AES) (FIG. 3), but also come from the adjacent rostro-lateral suprasylvian sulcus, (rLS)[31–37]. The existence of similar circuits in other species remains to be determined. When the AES is deactivated, its target neuron in the SC might retain its multisensory character, but the response to the cross-modal stimulus is no longer more effective than its response to its modality-specific component stimuli. This loss of physiological integration is coupled with a loss of the SC-mediated behavioural benefits that are associated with multisensory integration.

It seems reasonable to expect that every multisensory neuron would be capable of synthesizing its inputs from different sensory modalities regardless of their source. Surprisingly, this is not the case, at least not in the cat SC. The descending cortical neurons from the AES are unisensory and they converge on an SC neuron in a way that matches the sensory profile that it acquires from other sources. A visual–auditory SC neuron, for example, will receive visual inputs from the anterior ectosylvian visual area (AEV) and auditory inputs from the auditory field of the anterior ectosylvian region (FAES)[38]. These excitatory inputs, along with some hypothetical inhibitory elements which are also predicted by a new computational model that helps us understand the relative contributions of ascending and descending inputs from different senses to the production of a multisensory response[39] (see also REF. 40), are shown in FIG. 3b. Some of the model's predictions are based on sensory terminal patterns, membrane channels and receptor clusters that remain to be demonstrated in SC neurons. Gaining further information on these aspects of SC neuron physiology and how they develop during postnatal life (BOX 3) might thus aid future research into the biophysical mechanisms that are engaged in this circuit during multisensory integration.

Inverse effectiveness
The phenomenon whereby the degree to which a multisensory response exceeds the response to the most effective modality-specific stimulus component declines as the effectiveness of the modality-specific stimulus components increases.
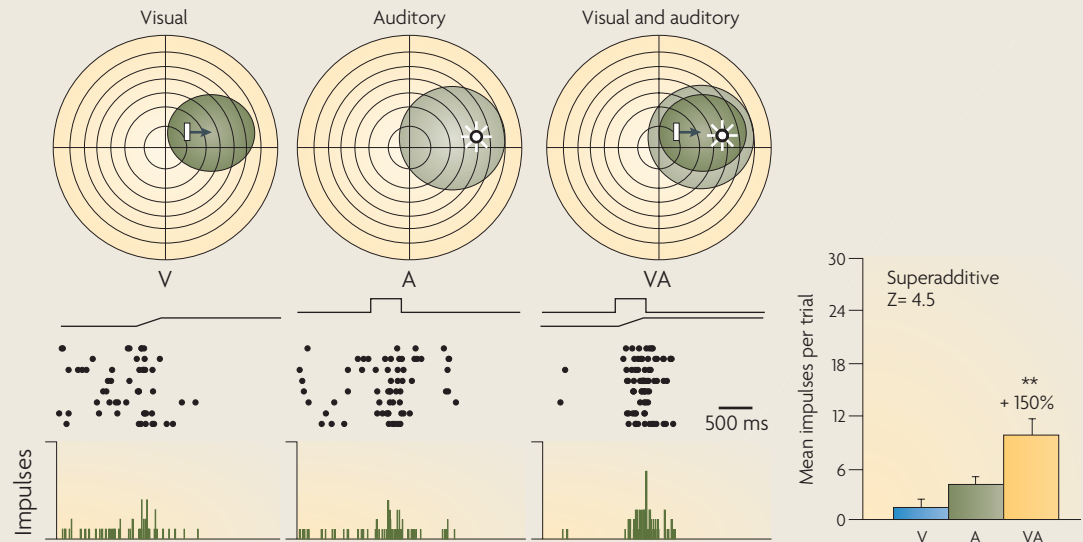
Multisensory integration in the cerebral cortex
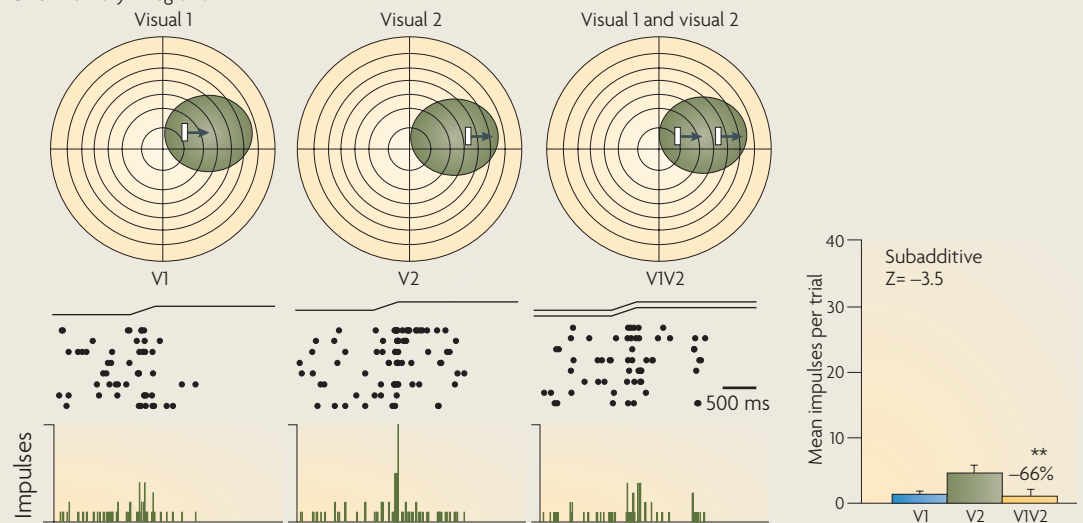In addition to the cerebral cortex of the cat, neurophysiological and functional-imaging studies have identified many 'multisensory' cortical regions in both humans and non-human primates (FIG. 4). Although few neurophysiological studies in non-human primates have demonstrated multisensory integration as it is operationally defined, there seems little doubt that many of

Box 2 | **Is multisensory integration different from unisensory integration?**

a Multisensory integration

Visual | Auditory | Visual and auditory

V | A | VA

Superadditive
Z= 4.5
**
+ 150%

Mean impulses per trial

500 ms

Impulses

b Unisensory integration

Visual 1 | Visual 2 | Visual 1 and visual 2

V1 | V2 | V1V2

Subadditive
Z= −3.5
**
−66%

Mean impulses per trial

500 ms

Impulses

It is interesting to note that until very recently one of the most fundamental tenets of multisensory integration remained unexplored: whether or not the computations that underlie the integration of stimuli from different senses (multisensory integration) and those from the same sense (unisensory integration) are fundamentally the same. In the absence of empirical data, it had been impossible to distinguish between these two mutually exclusive but equally plausible alternatives, which have very different implications for the processes that underlie the integration of information (regardless of its source). However, it is now known that, at least in some neurons, the computations are fundamentally different[35]. The figure shows multisensory and unisensory integration in a multisensory superior colliculus neuron. The visual and auditory receptive fields of this neuron and the positions of the stimuli are shown within visual and auditory space. In panel **a**, weakly effective visual and auditory stimuli (represented by the electronic traces) are integrated to produce multisensory enhancement. In this case, the enhanced combined response exceeds the sum of the component responses (see histogram) and was therefore superadditive. It is important to note that, in principle and in practice, enhanced responses could be superadditive, additive or subadditive. In panel **b**, pairing the visual stimulus with another visual stimulus yields a subadditive interaction that fails to meet the criterion for enhancement. These representative samples are exemplary of the characteristic differences between the neural computations that underlie multisensory and unisensory integration. Figure reproduced, with permission, from REF. 35 © (2007) Cambridge University Press.

Additivity
A neural computation in which the multisensory response is not different from the arithmetic sum of the responses to the component stimuli.

Subadditivity
A neural computation in which the multisensory response is smaller than the arithmetic sum of the responses to the component stimuli.
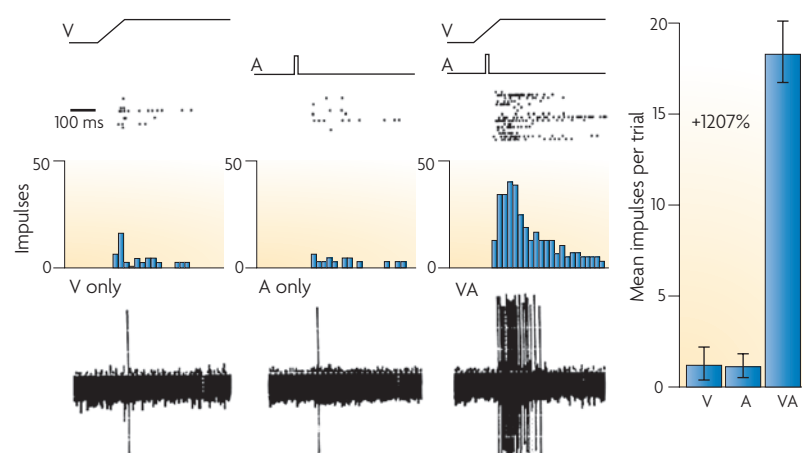
Figure 2 | **Multisensory enhancement in a single superior colliculus neuron.** Depiction of visual (V), auditory (A) and combined (VA) stimuli, impulse rasters (in which each dot represents a single neural impulse and each row represents a single trial), peristimulus time histograms (in which the impulses are summed across trials at each moment of time and binned), single-trace oscillograms and a bar plot depicting the response of a superior colliculus (SC) neuron to the stimulation. Note that the multisensory response greatly exceeds the response to the either stimulus alone, thereby meeting the criterion for multisensory integration (that is, response enhancement). In this case, however, the integrated response exceeds the sum of the component responses, revealing that the underlying neural computation that is engaged during multisensory integration is superadditivity. Figure reproduced, with permission, from REF. 26 © (1986) Cambridge University Press.

these regions contain neurons that would be capable of integrating cross-modal cues. Here we consider studies of the cat AES cortex, followed by results from both non-human primates and humans that extend our discussion of multisensory integration beyond the simple orienting behaviour described above to more complex forms of multisensory coding.

Along with its SC-projecting unisensory neurons, the cat AES contains multisensory neurons that do not project to the SC[38] — their circuitry remains to be determined. This counterintuitive observation (one would expect multisensory neurons in interconnected structures to interact) became even more surprising when it was found that these neurons integrate inputs from different senses in many of the same ways that SC neurons do[41,42]. Indeed, many of the properties of multisensory neurons in the AES and the SC are similar[42]. For example, spatial register of the modality-specific receptive fields of multisensory neurons is an essential feature of neurons in both structures. Spatially disparate stimuli are either not integrated or produce multisensory depression, although this effect might be less potent in the AES than in the SC. AES multisensory enhancement also requires temporal concordance and exhibits inverse effectiveness. Given their many parallels, it is tempting to conclude that multisensory neurons in the SC and the AES have similar functions. However, it is not known whether multisensory AES neurons target regions that are involved in orienting behaviours.

Unfortunately, few other cortical areas have been the subject of studies that assess the capacity of constituent neurons to integrate inputs from different senses. For

example, few studies have considered the effect of spatial coincidence or disparity on the products of integration in other cortical areas. Nevertheless, determining the spatial relationship among a neuron's modality-specific receptive fields will be of paramount importance in understanding the neural computations that are performed within a given region. Rather than the AES (for which the primate homologue is unknown), in primates such studies have focused on the posterior parietal cortex (PPC), where sensory information from many different modalities (visual, vestibular, tactile and auditory) converges.

The brain's huge energy investment in aligning sensory maps during development and in keeping them aligned during overt behaviour is amply rewarded. Because different unisensory neurons contact the same motor apparatus, map alignment is critical for coherent behavioural output, even in the absence of multisensory integration. Moreover, sensory-map alignment also sets the stage for the spatial principle of multisensory integration and the behavioural benefits that it supports.

Keeping receptive fields aligned in the posterior parietal cortex. In primates, the PPC is composed of subregions that are involved in various aspects of spatial awareness and guidance of actions towards spatial goals. Prominent among these are the lateral intraparietal (LIP), medial intraparietal (MIP) and ventral intraparietal (VIP) areas (FIG. 4a). The PPC transforms sensory signals into a coordinate frame suitable for guiding either gaze or reach. For example, LIP neurons encode visual and auditory stimuli with respect to current eye position, a reference frame that is appropriate for computing the vector of a gaze-shift towards a visual, auditory or cross-modal goal[43]. This requires auditory receptive fields to be dynamic, as they must shift with each eye movement (FIG. 5). In the parietal reach region (PRR), a physiologically defined region that includes part or all of the MIP, visual or auditory targets are likewise encoded in a common eye-centred coordinate scheme[44,45]. However, the PRR is responsible for producing goal-directed limb movements, and an eye-centred representation does not directly specify the spatial relationship between an object of interest and the necessary limb movement to reach it. The implications of this more abstract representation are beyond the scope of this Review (but see REFS 46,47), but it should be noted that many areas of the brain have a mechanism for creating, and dynamically maintaining, a spatial correspondence between stimuli from different modalities. Although multisensory integration has not been explicitly examined in either the LIP or the MIP, such re-mapping into common coordinate frames would be a prerequisite if multisensory enhancement and depression were to adhere to the same spatial rules that are apparent in the SC and the AES.

Despite its simplifying appeal, there is evidence to suggest that reference-frame re-mapping is often incomplete. It is not uncommon to observe neurons that have receptive fields that shift only partially with changes in eye position and that code information in an intermediate reference frame[48–51]. The presence of such neurons
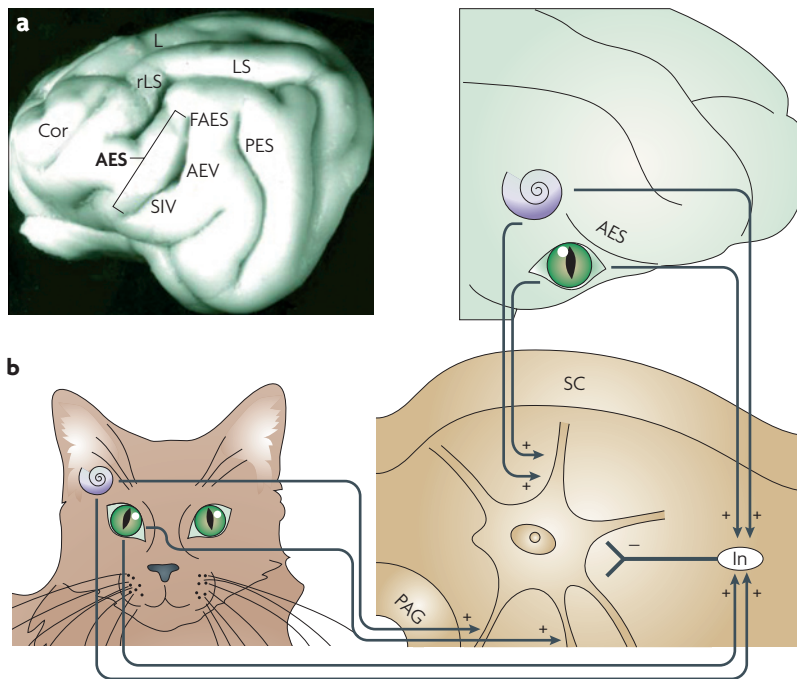
Figure 3 | **Superior colliculus multisensory integration depends on the cortex.**
a | A view of the cat brain, showing the anterior ectosylvian sulcus (AES). The somatosensory (SIV, the fourth somatosensory area), visual (AEV, the anterior ectosylvian visual area) and auditory (FAES, the auditory field of the AES) regions of the AES are shown (see REF. 106 for further details). **b** | Schematic of the visual–auditory convergence onto a superior colliculus (SC) neuron from ascending and descending sources. Descending influences derive from the visual and auditory regions of the AES. The hypothetical convergence pattern is predicted by a computational model of multisensory integration, in which only descending inputs target electrotonically coupled areas of the target neuron in the SC. All inputs also project to interneurons (In) that project to the multisensory output neuron. Cor, coronal sulcus; L, lateral sulcus; LS, lateral suprasylvian sulcus; PAG, periaqueductal grey; PES, posterior ectosylvian sulcus; rLS, rostral LS. Part **b** modified, with permission from REF. 39 © (2007) Pion.

seems to be the rule rather than the exception in cortical areas, and this might also be true in the SC[20–22]. It has been argued, on the basis of neural-network simulations, that these neurons could serve as essential elements in a network that enables efficient transformation from one coordinate frame (for example, eye-centred) to another (for example, head-centred)[48,52]. For multisensory integration, the primary implication of such incomplete receptive-field shifts would be that spatially congruent cross-modal stimuli would not necessarily fall simultaneously within the individual receptive fields of any given neuron. For such neurons, the spatial register of modality-specific receptive fields would vary with changes in eye position, as has been shown in the VIP[49]. Thus, the probability of observing multisensory enhancement should also vary, although this has yet to be tested empirically in any structure. To date, only one study of VIP neurons has explicitly examined multisensory integration, and it did so with the eyes and head aligned[53]. Interestingly, this study showed that spatially congruent visual–tactile stimuli were just as likely or more likely to evoke multisensory depression as enhancement, suggesting that there is a higher degree of complexity in the cortex than there is in the SC.

The importance of stimulus congruence. The complexity of cortical multisensory representations is further emphasized by considering the integration of non-spatial information. This is particularly germane to communication, as semantic congruence between sight and sound is more important than stimulus location[54]. Single-neuron studies have only recently begun to explore this aspect of multisensory integration. In one study[55], the responses of visual–auditory neurons in the superior temporal sulcus (STS) were quantified (FIG. 4a). Using monkey vocalizations that were either congruent or incongruent with facial movements depicted in video clips of human faces, the authors identified neurons for which responses to the visual images were modulated by the concurrently presented sounds. The sample size was small and multisensory integration was as likely to produce depression as enhancement. However, when enhancement was obtained, it was greater for congruent than for incongruent pairings. More recently it was shown that a region of the ventrolateral prefrontal cortex (VLPFC) that receives input from the STS is dedicated to the multisensory integration of vocal communication signals[56,57]. This study also demonstrated more depression than enhancement in its sample of integrating neurons, and noted that multisensory integration was more commonly observed for face–vocalization pairs than for more generic visual–auditory pairings.

These single-neuron studies suggest a complexity of multisensory integration that is not observed in the SC, emphasizing that multisensory integration is not a unitary phenomenon. The principles of space and time, and their relationship to multisensory enhancement and depression, are more relevant to the SC, a structure that has evolved to detect and drive orientation to salient events. Because it is possible to orient to a single location at a time, it seems functionally imperative that spatially congruent stimuli reinforce each other (leading to multisensory enhancement) and spatially disparate stimuli compete (leading to multisensory depression). Different computational goals in the cortex might dictate different integrative principles.

Although discrete receptive fields and physical limits to temporal integration dictate that multisensory interactions in virtually all regions will be constrained by the spatial and temporal proximity of the stimulus components, the specific products of integration will necessarily reflect the particular functions to which the regions contribute. With this in mind, we note that the conceptualizations of regional cortical multisensory functions are at an early stage. In many cases the computational endpoints of cortical neurons are unclear, making the task of interpreting a diversity of multisensory outcomes difficult. Thus, for example, the contributions of multisensory enhancement and depression to the representation of congruent communication signals remain to be determined. Undoubtedly, the relationships between such integrative products and the computational goals that they support will become clearer as more studies are conducted and as their findings contribute to the development of more complete

Box 3 | Development of multisensory integration
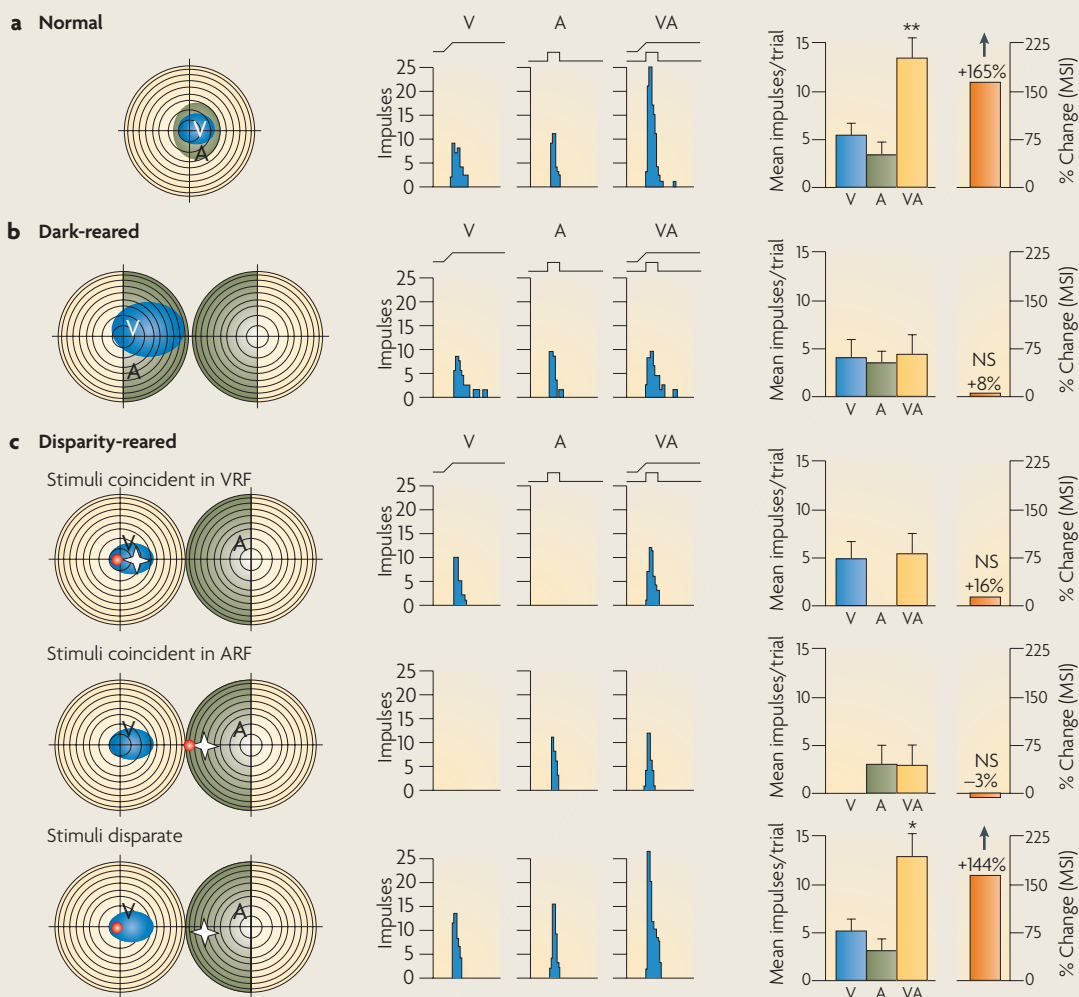
There has been long-standing speculation about whether multisensory integration requires postnatal maturation. Empirical studies have shown that, in the cat, neither superior colliculus (SC) nor anterior ectosylvian sulcus (AES) neurons have multisensory properties at birth[95–97]. Even when their multisensory character first becomes evident, cat neonatal multisensory neurons are incapable of generating enhanced multisensory responses. Similarly, although the monkey has multisensory neurons at birth, they too are incapable of synthesizing cross-modal inputs[98].

Studies in the cat SC have shown that integrative capacity develops in parallel with the functional maturation of inputs from the association cortex[99,100]. This process is protracted, providing the opportunity to acquire cross-modal sensory experience. Interfering with this process, by precluding normal visual–non-visual experience (dark rearing), also precludes visual–non-visual integration[101]. This is shown in parts **a** and **b** of the figure. Normally when visual (V) and auditory (A) stimuli are within the overlapping receptive fields of an SC neuron, the response is significantly enhanced (it exceeds that of the modality-specific component stimulus, +165% here). However, when an animal (in this case a cat) is raised in the dark (when it has no visual–non-visual experience), these spatially coincident stimuli do not produce enhanced responses.

In cats raised with exposure to visual–auditory stimuli that are linked in time but separated in space[102], some SC neurons formed visual–auditory receptive fields with little or no spatial register (figure, part **c**). In this case, spatially coincident stimuli (visual stimulus is indicated by the red circle, the auditory stimulus by the white star) cannot simultaneously fall within their respective receptive fields and do not enhance responses (top and middle of part **c**). Rather, there is a reversal of the normal spatial principle of multisensory integration, with spatially disparate visual–auditory stimuli producing enhancement (bottom of part **c**; +144%).

Data from recent studies confirms that this early experience is coded in the AES projections to the SC[33,103], thus explaining why descending influences have such a key role in facilitating multisensory integration in the adult; these projections are likely to mediate context-dependent changes in multisensory responses. A recent study[104] has shown that human babies are also delayed in their ability to integrate visual and auditory cues for spatial localization, suggesting that humans might also acquire visual–auditory multisensory integration only after substantial postnatal experience with these cross-modal stimuli. Likewise, humans deprived of pattern vision (by binocular cataracts) for the first months of life exhibit impaired visual–non-visual integration after removal of the cataracts[105]. ARF, auditory receptive field; MSI, multisensory integration; NS, not significant; VRF, visual receptive field. Bottom panel of part **c** is modified, with permission, from REF. 102 © (2007) American Physiological Society.
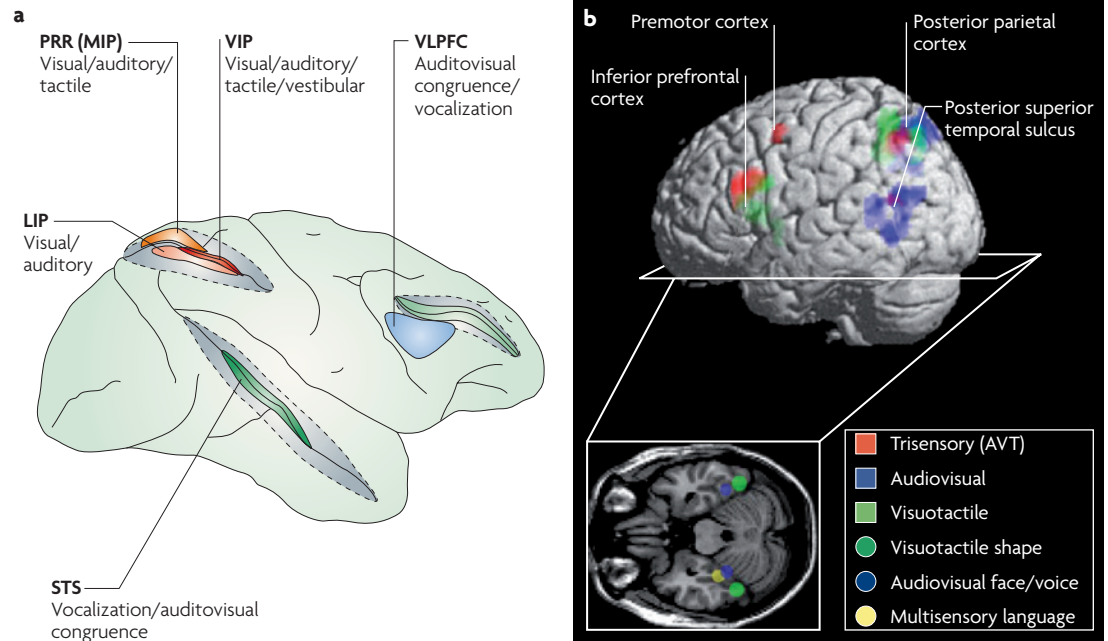
Figure 4 | **Multisensory regions in the monkey and human cortex. a** | Putatively multisensory regions of the monkey cortex. The coloured areas represent regions in which neurons that respond to multiple sensory modalities have been identified and include the lateral intraparietal area (LIP), the parietal reach region (PRR) in the medial intraparietal area (MIP), and the ventral intraparietal area (VIP), which is located at the fundus of the intraparietal sulcus, the ventrolateral prefrontal cortex (VLPFC) and the superior temporal sulcus (STS). Studies have shown that the visual, auditory and/or tactile receptive fields of single neurons in regions of the posterior parietal cortex can be encoded within a common reference frame. Single-neuron studies of the STS and the VLPFC have shown that multisensory neurons are sensitive to the semantic congruency of multisensory stimulus components. **b** | A rendering of the human brain showing putative multisensory regions, as defined by functional imaging criteria. Areas in which blood-oxygen-level-dependent (BOLD) activity related to visual, auditory and tactile stimuli was measured are shown. Red denotes brain regions in which the auditory, visual and tactile activations overlapped (trisensory or AVT regions); blue denotes regions in which the auditory and visual (audiovisual) activations overlapped; green denotes regions in which the visual and tactile (visuotactile) activations overlapped. The inset shows a horizontal section and identifies regions in which activations related to more complex multisensory stimuli (objects, communication and speech) have been measured. Part **b** modified, with permission, from *Neuron* REF. 107 © (2008) Elsevier Sciences.

Evoked-potential studies
Electrophysiological studies in which the electrical activity (that is, the electrical potential) of the brain in response to a stimulus is measured using scalp-surface electrodes.

Blood-oxygen-level-dependent (BOLD) signal
An index of brain activation based on detecting changes in blood oxygenation with functional MRI.

Superadditivity
A neural computation in which the multisensory response is larger than the arithmetic sum of the responses to the component stimuli.

Summation
A neural computation in which the response to a multisensory stimulus (for example, a number of action potentials) equals the sum of the responses to each of the modality-specific component stimuli presented individually.

conceptual frameworks. Such studies are likely to be aided by insights derived from functional-imaging studies in humans.

Studies in the human cerebral cortex. Most studies of multisensory processing in the human cortex come from neuroimaging and evoked-potential studies[6,58]. Local field potential (LFP) studies have revealed multisensory integration (enhancement and depression) in specific regions of the auditory cortex. Consistent with the results of single-neuron studies in the primate STS[55], and analogous to those in the primate VLPFC[56,57], multisensory interactions in the human auditory cortex favoured the integration of stimulus pairs containing conspecific face and vocal clips[59]. These findings are generally consistent with earlier human neuroimaging studies suggesting that the STS is specialized for integrating auditory and visual speech signals[60]. In these studies, the blood-oxygen-level-dependent (BOLD) signal was enhanced for congruent pairings of audible speech and lip movement and depressed for incongruent pairings, suggesting that interactions in the STS underlie the well-documented effects of multisensory integration

on improving (congruent) or degrading (incongruent) speech intelligibility[60].

The STS is perhaps unique in that evidence from multiple studies supports a similar conclusion. However, whether or not multisensory integration also occurs for non-speech stimuli in the STS has been the subject of debate. It has been argued that the BOLD response for cross-modal stimuli must exceed the sum of the BOLD responses to the modality-specific components if multisensory integration is to be conclusively established[61]. This superadditivity requirement recognizes that lesser enhancements (such as simple summation) could reflect the independent contributions of neighbouring unisensory neurons and not true multisensory convergence. We also note here that there is evidence to suggest that the BOLD response only weakly reflects postsynaptic activity and that it is therefore unlikely to be directly analogous to results from single-neuron studies (see REF. 62 for a review).

This stringent criterion eliminates false positives; however, it almost inevitably leads to misses[63], leading some researchers to promote the use of less restrictive statistical criteria[64]. This approach has led to the conclusion that the

STS integrates information about a variety of common cross-modal objects[65]. However, although such studies reveal potential foci of multisensory interactions, they cannot be considered definitive and have to be considered in light of corroborating evidence. In an attempt to conclusively establish integration for non-speech stimuli in the STS, one study used cross-modal combinations composed of stimulus components that were near the threshold for detection[66]. The logic of this approach was based on the rule of inverse effectiveness, which dictates that combinations of the weakest stimuli produce the largest relative enhancements in the activity of multisensory neurons[26] (thus, superadditive interactions are most likely to occur[3,12,27,28]). Moreover, the use of weak cross-modal stimuli reduces the possibility that their combination saturates the BOLD response. This study demonstrated superadditivity in the STS for common auditory-visual objects and argues in favour of a more general multisensory role for the region.

Is the concept of a unisensory cortex still useful?

Functional imaging studies have identified numerous putatively multisensory regions in all cortical lobules (FIG. 4b). This conflicts with the classical view of sensory organization, in which multisensory interactions arise from the late-stage convergence of segregated modality-specific cortical streams. Studies have demonstrated multisensory influences on activity within classically defined unisensory domains, including relatively low-order regions of sensory cortices (see REF. 58 for a review). One interpretation, for which there is ample evidence (see REF. 67 for a review), is that these influences represent feedback from higher-order cortical territories. This suggests that top-down influences could affect relatively early sensory encoding, which in turn could underlie a host of well-documented multisensory attentional effects[4,6,68,69]. A more provocative interpretation is that these influences are not due solely to feedback from higher cortical areas, but that instead they are carried by feedforward pathways that support multisensory integration at very early stages in the cortical processing hierarchy. This view received early support from an event-related potential (ERP) study[70], which provided evidence of auditory–visual interactions in the visual cortex less than 50 ms after stimulus onset. Interactions that take place too early to be due to feedback have since been reported for other 'unisensory' cortices[67,71]. The functional significance of such early interactions between the senses is yet to be established, however, one intriguing hypothesis is that they have an important role in input binding[67]. Functional implications notwithstanding, evidence of early multisensory convergence raises fundamental questions about the sensory-specific organization of the cortex.

The observations that many areas that were previously classified as unisensory contain multisensory neurons are supported by anatomical studies showing connections between unisensory cortices[72–76] and by the many imaging and ERP studies that reveal multisensory activity in these regions. These observations question whether there are any exclusive, modality-specific
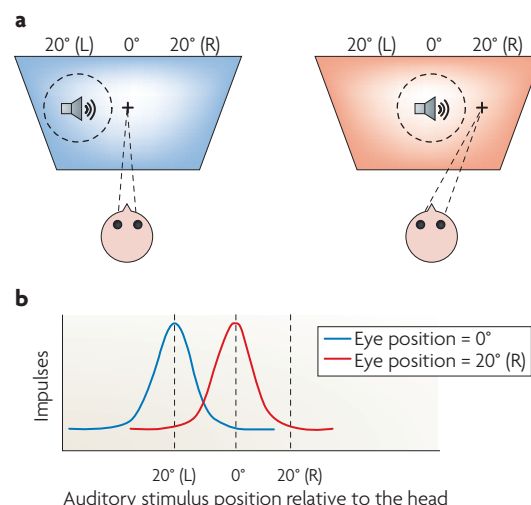
Figure 5 | **Shifting receptive fields are relevant to multisensory integration.** A hypothetical auditory receptive field shown in eye-centred coordinates. **a** | The position of an auditory receptive field (dotted circle) when the eyes are directed ahead (left panel) and when the eyes are deviated 20° to the right (right panel). With the change in the angle of gaze, the receptive field shifts from 20° to the left of the head to 0° relative to the head. In doing so, it maintains a constant spatial relationship to the direction of gaze: in eye-centred coordinates the auditory receptive field is always 20° to the left of the gaze. **b** | Response magnitude as a function of the auditory stimulus position with respect to the head for each of the two gaze angles. The figure depicts a complete shift, one that compensates fully for changes in gaze angle. Examples of such neurons have been found in many regions, including the superior collicus and the lateral intraparietal area. However, partial shifts are also common. Although this figure illustrates auditory information in eye-centred coordinates, the concept generalizes to all sensory modalities and reference frames. L, left; R, right.

cortical regions and, thus, whether it is worth retaining designations that imply such exclusivity. Does this growing certainty that inputs from a second (or third) sensory modality access a unisensory cortex warrant a change in current cortical parcellation schemes? Such a change would radically alter concepts of how the cortex is organized and how research to understand the cortex's functional properties is conducted. The issue is complicated by a host of other questions. It is important to define the criterion incidence of modality convergence that warrants designating a region 'multisensory'. It is also important to understand the functional impact of the cross-modal input(s). Armed with this knowledge, it will be possible to consider the value of changing well-established modes of categorization.

Unfortunately, there is no generally accepted criterion incidence for designating a cortex 'multisensory'. Furthermore, there is considerable variability in estimates of the incidence of non-matching inputs (that is, inputs that don't match the predominant sensory representation) in cortical regions that have traditionally been defined as unisensory. The estimates of non-matching

neurons in presumptive unisensory cortex vary from less than 8% to 50% or more[72,77–81]. In part, this is due to differences in the experimental techniques that are used and in the particular regions of the cortex that are being scrutinized. In one study, the comparative modality convergence patterns were examined in the rat[78]. The results revealed large expanses of visual, auditory and somatosensory cortices, with comparatively few neurons (less than 8%) that are responsive to other sensory stimuli. However, the borders between two sensory representations contained a mixture of unisensory neurons from both modalities and a far higher than average incidence of multisensory neurons. The existence of such multisensory transitional zones[41,72,82] might affect interpretations of some (but not all[58]) of the results from studies using methods that provide lower spatial resolution.

Nevertheless, primary areas are generally thought to contain fewer non-matching neurons than surrounding cortices. Interestingly, the multisensory neurons noted within and bordering sensory areas discussed above were able to integrate their inputs from different senses in much the same way that SC and AES neurons do. The authors of this study[78] concluded that the comparatively small number of non-matching inputs did not warrant eliminating the current designation of 'unisensory' cortex, but instead suggested adding a designation for the transitional zones between unisensory regions, where neurons integrate their cross-modal inputs in much the same way that SC and AES neurons do.

The sensory reports of patients undergoing direct cortical stimulation are also in keeping with the current designation of unisensory cortices. Electrical stimulation of primary and secondary sensory cortex produces comparatively simple, sensory-specific sensations[83–86]. The only non-matching sensations referred to are linked to inadvertent electrical stimulation of the scalp or meninges. This result is very different from the complex sensations, memories and hallucinations produced by stimulation of other cortical regions[86], and is consistent with the seemingly sensory-specific perceptual effects of lesions in these areas.

Although it does not seem that a compelling case has yet been made for discarding traditional schemes of cortical organization, one question remains: what is the role of the non-matching sensory inputs that clearly do reach these unisensory regions and alter the responses of its constituent neurons? The question remains unresolved, but it might be that they somehow facilitate the unisensory functional role of each cortex — perhaps, as suggested for the auditory cortex[87], by resetting its ongoing activity to render it more responsive to subsequent sensory-specific input.

Concluding remarks

It is apparent from the discussion above that the field of multisensory integration is at an intermediate stage of development. We began this Review with a very brief summary of work that explored the neurophysiological underpinnings of multisensory integration in the cat SC. Although our understanding of this process continues to be refined, the most basic mechanisms of multisensory integration, and their implications for orienting to a sensory target, have been known for some time. However, we have entered a new era in which there has been explosive growth in both the number and the variety of investigations into multisensory phenomena; in this Review we have chosen to highlight a few areas of exploration that are likely to help define the field going forward.

In particular, the issue of coordinate frameworks for representing sensory information, which has historically been discussed in the context of re-mapping sensory information for the purpose of generating motor output, is an inherently multisensory problem. How brain areas like those in the PPC maintain, or fail to maintain, register of modality-specific representations has profound implications for multisensory integration and the spatial rules to which it seems to adhere. Likewise, investigators have only begun to consider the issues relating to deciphering the neural representations of higher-order multisensory phenomena, such as speech perception and multisensory semantic congruency. Unlike the simple interplay between excitation and inhibition that is necessary to create topographic maps of stimulus location and movement metrics, the coding dimensions for these higher-order functions are undoubtedly much more complex. Understanding the functional roles of these brain regions that are capable of integrating information from different senses is a necessary prelude to understanding how the brain coordinates their contributions to perception and behaviour.

Understanding the principles that govern these more complex multisensory functions will require strong correlative evidence from human imaging studies and from single-neuron studies in animals. We have only alluded to the difficulty in relating the results obtained from these distinct methodologies; although the same terms are commonly used (such as multisensory enhancement or superadditivity), we should be aware of the fact that the mapping between the BOLD response and the activity of single neurons is an area of open inquiry.

Finally, it is not immediately apparent how the field will come to a consensus on what constitutes a multisensory (as opposed to a unisensory) region. The issue is far from settled and definitive criteria are not as readily apparent as it might seem. Determining how information from a non-matching sense modality alters the information processing in a classically defined unisensory domain will be crucial for understanding multisensory integration.

Although there are many outstanding issues, it is important to note that progress in the field has been impressive. A great deal has been learned about multisensory integration at the individual-neuron and neuronal-network levels, the principles that govern multisensory integration, its impact on behaviour and perception, and the maturational and experiential requirements for its acquisition during early life. The rapid growth of this young field, the excitement that it generates and the impressive armamentarium available to its practitioners provide confidence that the best is yet to come.

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