The multisensory function of the human primary visual cortex

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ABSTRACT

It has been nearly 10 years since Ghazanfar and Schroeder (2006) proposed that the neocortex is essentially multisensory in nature. However, it is only recently that sufficient and hard evidence that supports this proposal has accrued. We review evidence that activity within the human primary visual cortex plays an active role in multisensory processes and directly impacts behavioural outcome. This evidence emerges from a full pallet of human brain imaging and brain mapping methods with which multisensory processes are quantitatively assessed by taking advantage of particular strengths of each technique as well as advances in signal analyses. Several general conclusions about multisensory processes in primary visual cortex of humans are supported relatively solidly. First, haemodynamic methods (fMRI/PET) show that there is both convergence and integration occurring within primary visual cortex. Second, primary visual cortex is involved in multisensory processes during early post-stimulus stages (as revealed by EEG/ERP/ERFs as well as TMS). Third, multisensory effects in primary visual cortex directly impact behaviour and perception, as revealed by correlational (EEG/ERPs/ERFs) as well as more causal measures (TMS/tACS). While the provocative claim of Ghazanfar and Schroeder (2006) that the whole of neocortex is multisensory in function has yet to be demonstrated, this can now be considered established in the case of the human primary visual cortex.

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1. Introduction

Until recently, the archetypical view of sensory organisation was that multisensory integration is a process that is restricted to higher-order brain regions and occurs only after substantial information processing within lower-level and sensory-specific cortices. As such, regions like primary visual cortex had traditionally been considered as exclusively visual in their function. Multisensory research has ushered a new view of brain organisation and perception, wherein the convergence and integration of information from different senses within low-level cortices is a rule rather than an exception (e.g. Ghazanfar and Schroeder, 2006; van Atteveldt et al., 2014a; de Meo et al., 2015; ten Oever et al., 2015) (Fig. 1). This new view is supported by multiple sources of evidence coming from studies involving various experimental paradigms, populations/species, as well as brain mapping methods. One consequence of this new view is that it is no longer accurate to functionally characterise primary visual cortex as exclusively visual, but rather as inherently multisensory.

This new characterisation, however, is considered by some to be controversial. The principal issue is to what degree multisensory effects in primary cortices are the first cortical loci of multisensory processes or instead simply a downstream by-product of multisensory processes elsewhere. A corollary controversy is therefore to what extent multisensory processes in primary cortices are directly affecting behaviour. In what follows, we address these controversies and review the current evidence for the multisensory nature of the primary visual cortex in humans (see Kayser et al. (2009) for auditory cortex). To facilitate a response to the above controversies, we focus here in large part on studies using simple, rudimentary stimuli (e.g. flashes/checkerboards and tones/noises). Some advantage of using such stimuli include: (1) catalysing inter-species generalisations, (2) they are a

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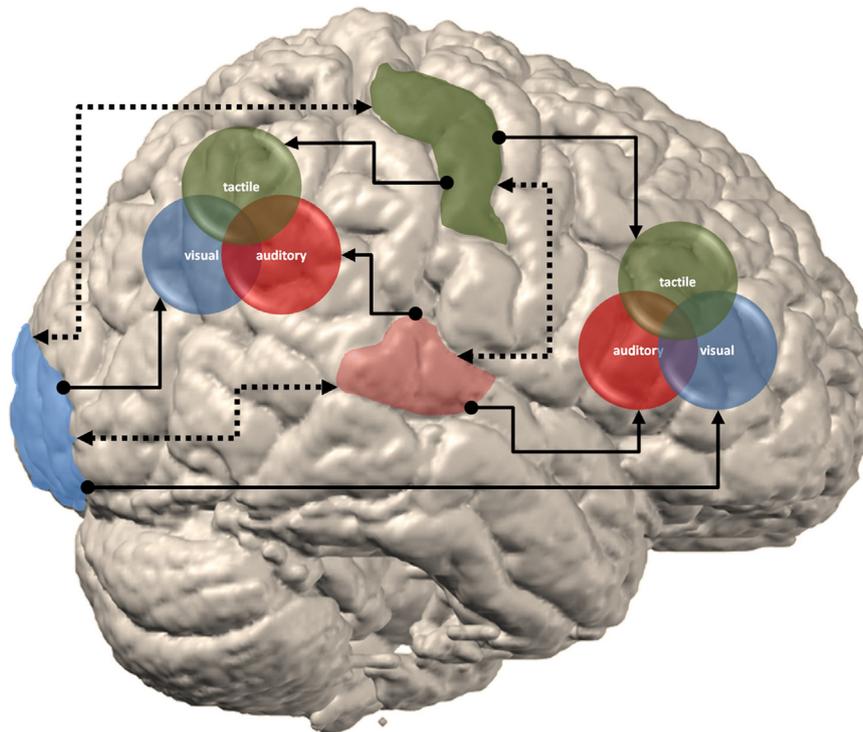E-mail addresses: micah.murray@chuv.ch (M.M. Murray), pawel.matusz@chuv.ch (P.J. Matusz).

Fig. 1. Schemas of cortical loci of multisensory processes. The schemas are depicted on a right hemisphere, with the occipital lobe on the left side of the image and the frontal lobe on the right side. Low-level visual, auditory, and somatosensory (tactile) cortices are indicated by the blue, red, and green shaded regions, respectively. The solid lines depict a schema where interactions are restricted to higher-order association cortices, such as the prefrontal and parietal cortices (indicated by superimposed coloured discs). The dotted lines depict a schema where interactions occur directly between low-level cortices. There is now evidence in support of both schemas. Therefore, multisensory processes undoubtedly involve a dynamic combination of these schemas that probably emerge as a consequence of experience-dependant processes. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

reasonable starting point for addressing controversies in how to identify and qualitatively describe multisensory phenomena, and (3) their properties can be parametrically varied to render them physically (and therefore perceptually and/or behaviourally) more complex and ethologically more valid (e.g. Ghazanfar et al., 2005; Cappe et al., 2009b; see also Fort et al. (2002a,b) for effects of parametric variation of task demands).

2. The anatomic scaffolding for multisensory processes in the primary visual cortex

One line of support for the view of the primary visual cortex as the locus of multisensory processes is based on anatomical evidence for monosynaptic afferents from primary and/or low-level auditory association cortices in monkeys (Falchier et al., 2002, 2009; Rockland and Ojima, 2003; Cappe and Barone, 2005; see also Clarke and Innocenti (1990), Clemo et al. (2008) for evidence in cats, Vaudano et al. (1991) for evidence in rats, Laramée et al. (2011, 2013) for evidence in mice; and Henschke et al. (2015) for evidence in Mongolian gerbils). These direct pathways complement the poly-synaptic pathways via higher-order association cortices as well as cortico-thalamo-cortical pathways (e.g. Cappe et al. (2009a); see also Smiley and Falchier (2009) and Meredith et al. (2009) for reviews). The current evidence further indicates that these connections follow a feedback-like laminar profile, originating and terminating in layers 6 and layers 1/6, respectively (Rockland and Ojima, 2003; Clavagnier et al., 2004). Finally, some have claimed that these projections are heterogeneously distributed across the retinotopic representations within the primary visual cortex, with more peripheral visual field representations receiving denser projections (Falchier et al., 2002; Rockland and Ojima, 2003). However, projections to neurons representing the

central visual field should not be discounted (detailed below). In humans, comparable anatomic tracing data are unavailable. For one, the tracer substances used in human tissue themselves migrate over distances of only a few centimetres and thus permit an evaluation of intrinsic but not long-range connectivity (Tardif and Clarke, 2001; Marguiles et al., 2009). Second, while focal lesions provide an opportunity to study long-range connections, the lesions must be limited to the grey matter to offer firm evidence regarding the sources of fibre tracts; a situation that is extremely rare (e.g. Di Virgilio and Clarke (1997) for a demonstration of heterotopic interhemispheric connectivity between the right inferior temporal cortex and both Wernicke's and Broca's areas). An alternative method to detail the anatomic connectivity in humans is offered by non-invasive diffusion-based imaging. While it has one major benefit in that it can be conducted in vivo (and therefore correlated with functional measures), the majority of diffusion-based parameters is qualitative in nature and provides no direct quantification of the axonal or other morphological properties of the underlying anatomy (Lemkaddem et al., 2014; Dauguet et al., 2007).

Such limitations notwithstanding, there is a growing number of studies reporting the presence of connectivity between the primary visual cortex and primary auditory cortex (as well as other higher-level visual and auditory cortices). For example, in a pair of studies, Beer et al. (2011, 2013) have reported the existence of fibre tracts between a seed region within the Heschl's gyrus and the occipital pole as well as the anterior portions of the calcarine sulcus. Additional tracts were found between the planum temporale and both the occipital pole as well as anterior portions of the calcarine sulcus. Notably, the size of connected regions within the occipital pole and anterior calcarine sulcus were comparable (Beer et al., 2011). This pattern suggests that both central and peripheral visual field representations receive projections from

primary and low-level auditory cortices. Resolving the discrepancy between the abovementioned studies in humans and those carried out in animal models is undoubtedly one major challenge for the nearest future. Nonetheless, what is important to note is that both lines of research converge in demonstrating the presence of auditory inputs to the primary visual cortex.

Data from blind and visually-impaired individuals as well as from animal models of visual deprivation provide another line of evidence in favour of multisensory congruence and interactions within the primary visual cortex (e.g. reviewed in Bavelier and Neville (2002), Sadato (2006), Renier et al. (2014), and Ricciardi et al. (2014)). These effects include both auditory as well as haptic responses within visual cortices. For example, primary visual cortex appears to be causally linked to the accuracy of reading Braille by early-blind individuals (Cohen et al., 1997, 1999; Sadato et al., 2002) and to also correlate with performance on tasks completed either via touch or sound (e.g. Amedi et al., 2003; Raz et al., 2005; reviewed in Ricciardi et al. (2014)).

The studies reviewed above provide strong evidence that there is anatomic scaffolding that would permit multisensory processes within the primary visual cortex. In what follows, we review functional evidence that multisensory processes are indeed occurring within these loci. First, however, we address a major, historical obstacle; namely the appropriate quantification of multisensory processes.

3. The challenge of quantifying multisensory and cross-modal responses in human brain imaging and brain mapping studies

A particular challenge in human multisensory research that involves brain imaging methods, such as functional magnetic resonance imaging (fMRI) or event-related potentials/fields (ERPs/ERFs), is determining the appropriate statistical criterion for identifying multisensory interactions within primary cortices as well as throughout the brain (originally reviewed in e.g. Calvert (2001), Beauchamp (2005) and Laurienti et al. (2005)). One major problem is the difficulty in transposing established principles of multisensory processing, defined on the basis of single-unit recordings in animals (Stein and Meredith, 1993), to population-level responses (and behaviour) in humans. Another difficulty is related to the ability to differentiate between and understand the nature of super-additive and sub-additive nonlinear responses, i.e. multisensory responses that are greater than or less than the summed unisensory responses, respectively (see Laurienti et al. (2005) for models based on the extrapolation of single-unit findings; also see below). Yet another persisting major controversy concerns the applicability of a linear model (i.e. the response to a multisensory pair is contrasted with the summed responses to the constituent unisensory signals presented in isolation) to data from human brain imaging. Several recent reviews have treated these issues in detail (e.g. Murray et al., 2012; Stevenson et al., 2014; Besle et al., 2004).

In the case of haemodynamic imaging, there is still no general consensus or an objective metric by which one could assert that a given statistical criterion is more robust at identifying multisensory brain activity than others. Some favour using a non-linearity criterion (e.g. Calvert, 2001). Others suggest comparing multisensory responses to the mean or the maxima of the unisensory responses (e.g. Beauchamp, 2005). Still, others propose using inverse effectiveness (i.e. presence of stronger multisensory responses for multisensory stimuli involving weak unisensory signals) as a hallmark of multisensory integration (James et al., 2012). The fundamental problem in identifying the presence of multisensory processes using haemodynamic imaging methods lies in the fact that these methods cannot differentiate within a

given voxel between populations composed of truly multisensory neurons versus a mixture of unisensory neurons (cf. Fig. 1 in Laurienti et al. (2005)). One solution is to analyse the temporal rather than the strength aspects of the neural response provided by haemodynamic brain imaging methods (see below).

Analyses of electromagnetic signals at the scalp provide particularly strong evidence regarding the presence of multisensory processing because of their sub-millisecond temporal resolution, especially when combined with knowledge regarding signal propagation in different sensory systems (e.g. reviewed in Murray and Spierer (2009), and Musacchia and Schroeder (2009)). An advantage of temporal information (i.e. when interactions occur) is that it helps to constrain where these interactions take place based on knowledge regarding how far throughout spatio-temporal hierarchies signals from each sensory modality have propagated. While it is undeniably true that the anatomic circuitry and their shaping by experience are prerequisites for multisensory processes, only functional studies can provide direct evidence for the presence of multisensory interactions within the primary visual cortex. In spite of this, ERP/ERF studies of multisensory processes have traditionally been criticised on two levels.

The first criticism, shared with haemodynamic methods, concerns the appropriateness of the additive model. While biophysical principles clearly describe how electric fields summate at the scalp level (e.g. Besle et al., 2004), there are valid concerns regarding the potential confound of common activity within the additive model (Teder-Sälejärvi et al., 2002). The second line of critique focuses more on signal processing and its consequences for statistical outcomes. Some researchers have demonstrated the impact of digital filters and baseline correction procedures (Teder-Sälejärvi et al., 2002), whereas others have scrutinised the fact that the latency, direction (super-additive vs. sub-additive), and scalp distribution of statistical effects involving voltage waveforms are entirely reference-dependant and therefore have very limited neurophysiologic interpretability (Cappe et al., 2010). The latter has been overcome by advances in signal processing techniques, which improve not only the capability to localise multisensory interactions, but also to provide a more mechanistic characterisation of their neurophysiologic bases (reviewed in Murray et al. (2008), Brunet et al. (2011), Michel and Murray (2012) and Koenig et al. (2014)). From a more mechanistic standpoint, the analyses falling under the umbrella-term of electrical neuroimaging (e.g. Murray et al., 2008) can reveal whether and, if so, when multisensory stimuli engage distinct configurations of brain regions and/or modulate the gain of regions already active under unisensory conditions. Moreover, the nature (i.e. directionality) of such effects can be determined; one can statistically distinguish between super-additive and sub-additive interactions, as a function of time.

Throughout this review we will discuss in more detail the approaches that enable one to circumvent, if not overcome altogether, the challenges in the quantification of multisensory processes in the human brain. In so doing, we will present how evidence from various sources supports multisensory convergence and integration within primary visual cortices in humans.

4. Haemodynamic imaging

Numerous haemodynamic imaging studies have documented auditory-visual convergence within primary visual cortices. For example, using a blocked design, Laurienti et al. (2002) reported deactivation within the primary visual cortex in response to sounds, but not if these sounds were accompanied by visual stimuli. However, in this and other, similar studies (e.g. Haxby et al., 1994; Kawashima et al., 1995) attention was explicitly directed

towards the visual stimuli, making it possible that top-down, goal-based attention to vision had obstructed positive-going activations and the corresponding multisensory effects (e.g. Mozolic et al., 2008).

Other studies have focused on brain activity occurring in the absence of external stimulation or task and have revealed the existence of intrinsic functional coupling between primary visual and primary auditory cortices (Eckert et al., 2008). Still others have likewise reported increased coupling between auditory and primary visual cortices, particularly under conditions of synchronous stimulation across the senses (Lewis and Noppeney, 2010; Tyll et al., 2013), that may perhaps be mediated by thalamic circuits (Noesselt et al., 2010; Bonath et al., 2013). In the same vein, sounds have been shown to activate visual cortices as a function of prior multisensory experiences (Zangenehpour and Zatorre, 2010; Meylan and Murray, 2007; see also Murray et al. (2004, 2005), Thelen et al. (2012, 2014); Matusz et al. (2015a) for effects of prior multisensory contexts on sensory processing). Such effects of multisensory exposure on visual cortex have been recently linked to the expression of immediate early genes (zif268) (Hirst et al., 2012). The same sound-induced visual cortex activations can be observed in humans also across a very short time scale using the so-called flash-beep illusion, wherein participants often report seeing two flashes when a single flash is presented close in time with two beeps (Shams et al., 2000). Watkins et al. (2006, 2007) have shown that activity within the primary visual cortex, more specifically the retinotopic representation of the veridical flash, is enhanced when a second flash is perceived and suppressed when two veridical flashes are perceived as one (see also Mishra et al. (2007) for comparable ERP results). de Haas et al. (2012) found

that grey matter volume in early human visual cortex predicts proneness to the flash-beep illusion. Notably, very recently, Vetter et al. (2014) demonstrated that it is possible to decode the category of natural sounds heard by participants based on the patterns of activity within the primary visual cortex (see also de Haas et al. (2013) for results of impaired decoding of visual stimuli within V2 in the presence of semantically incongruent sounds). Collectively, these findings provide strong evidence for a direct link between cross-modal responses in the primary visual cortex and perception (see also van Atteveldt et al. (2014b) for variations in multisensory processes as a function of task as well as across retinotopic representations).

To circumvent many of the analytical caveats of the analyses involving the blood-oxygenation level dependant (BOLD) signal amplitude, Martuzzi et al. (2007) studied multisensory processing within a simple detection task by focusing instead on the dynamics of the BOLD signal (Fig. 2, left). The study provided two main findings. The first critical finding was that auditory-visual multisensory convergence indeed occurs within primary visual cortices (as well as primary auditory cortices). The primary visual cortex exhibited robust responsiveness (i.e. non-zero BOLD signals) to auditory stimulation. It should be noted, however, that these cross-sensory responses were of significantly smaller magnitude than those to the visual stimuli. The second core finding was that primary visual cortices (and primary auditory cortices) were the locus of multisensory interactions. When the BOLD signal amplitude was analysed, responses to multisensory conditions within these regions were reliably sub-additive (although the inclusion of a motor task here makes it difficult to preclude the possibility that motor-related activity, even within primary
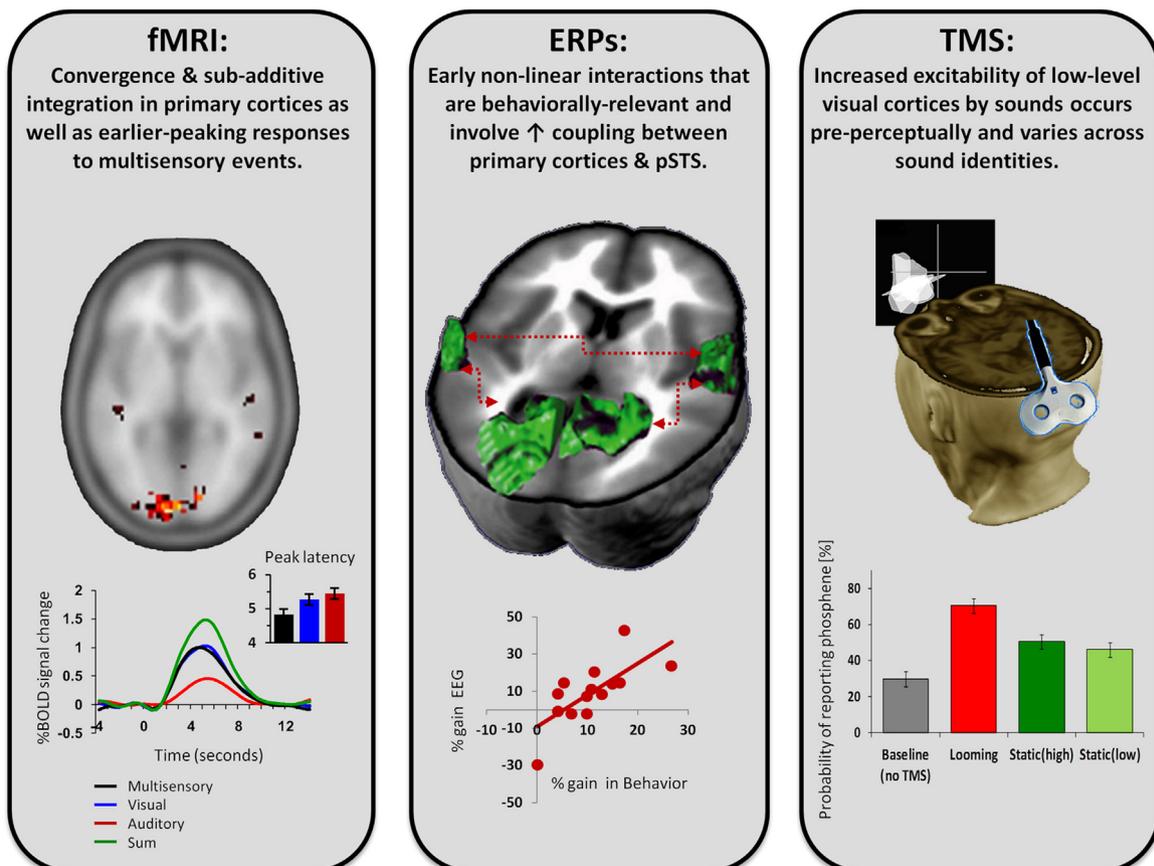

Fig. 2. Summary of findings concerning multisensory interactions between rudimentary stimulus features as studied with fMRI, EEG and TMS. Across methodologies, the data support multisensory convergence and interactions within primary visual cortices. Interactions within primary visual cortices are perceptually and behaviourally relevant. Data modified from Martuzzi et al. (2007), Cappe et al. (2010, 2012), and Romei et al. (2009).

sensory cortices, contributed to this sub-additive response). Importantly, also the dynamics of the BOLD response within primary cortices revealed that responses to multisensory and unisensory stimuli differed significantly from each other. Specifically, for the multisensory as compared to either unisensory condition within primary visual cortices (and primary auditory cortices) the BOLD signal peaked earlier (following also a steeper slope). Importantly, these latency effects were not a result of a simple amplitude/latency trade-off (see Table 1 in Martuzzi et al. (2007), for detailed statistics; see also Narsude et al. (2015) for a recent replication at 7T). A pressing issue that will require additional research is resolving the neurophysiologic mechanisms underlying modulations of the BOLD signal latency. One proposition is that an earlier peak reflects facilitated neural processing time (Henson et al., 2002; see Wang et al. (2008) for initial findings of facilitated responses latencies to multisensory stimuli in the monkey primary visual cortex). Notwithstanding, analyses of BOLD dynamics thus provide an important extension of the available repertoire of approaches for identifying brain regions involving multisensory processing using fMRI as well as putative neural mechanisms.

5. Electromagnetic signals (EEG/MEG)

The advances in the analysis of electromagnetic signals, falling jointly under the umbrella-term 'electrical neuroimaging framework' surmount many of the traditional caveats and interpretational limitations (see Michel et al. (2009), Murray et al. (2008, 2009), and Michel and Murray (2012) for recent, more detailed discussions).

To understand better the dynamics of multisensory processes gauged in perceptual tasks, we applied these analytical methods to ERPs in response to task-irrelevant AV stimuli that required top-down attention but no motor responses (Cappe et al., 2010; Fig. 2, centre). The core findings of this ERP study were the following: (1) nonlinear multisensory neural response interactions occurred as early as ∼60 ms post-stimulus onset, in line with other findings (*early multisensory integration, eMSI*; De Meo et al., 2015), (2) interactions followed from changes in the ERP topography rather than, simply, changes in the strength (gain) of the response, meaning that multisensory stimuli engaged distinct configurations of intracranial sources, (3) a network comprised of the primary visual cortex, primary auditory cortex, and the posterior superior temporal sulcus mediated these early interactions, (4) activity throughout this network was correlated under multisensory, but not unisensory stimulations, and (5) these nonlinear interactions were sub-additive both at the level of surface ERP topography and source estimations within specific brain regions.

The observed eMSI shared timing and scalp topography with the results of prior studies that involved task-relevant or passively presented stimuli (reviewed in De Meo et al. (2015)). These studies have typically reported multisensory interactions in the ERPs measured at individual electrodes onsetting ∼40–55 ms and visible as a parieto-occipital positivity in the difference map at the scalp (Fort et al., 2002a; Giard and Peronnet, 1999; Molholm et al., 2002; Vidal et al., 2008; Senkowski et al., 2011; Stekelenburg and Vroomen, 2012; Cappe et al., 2012; Altieri et al., 2015; see also Stevenson et al. (2012) as well as Barth et al. (1995) for corresponding data in the rat brain). The analysis of ERPs evoked by attended but task-irrelevant stimuli that required no motor response circumvented the caveat concerning motor-related activity (Gondan and Röder, 2006; Teder-Sälejärvi et al., 2002). Moreover, the varied inter-stimulus interval ensured that post-stimulus effects were not due to pre-stimulus anticipatory or state-dependant modulations (Teder-Sälejärvi et al., 2002). In another study, Cappe et al. (2012) demonstrated that these early non-linear interactions

could themselves be further enhanced by looming signals and that the extent of enhancement correlated with behavioural gains, thereby demonstrating the behavioural relevance of early multisensory processes. The robustness of the results of Cappe et al. (2010, 2012) further validates the suitability of an additive model to test for multisensory interactions (Besle et al., 2004). Because these results were obtained using reference-independent measures, their neurophysiologic underpinnings can be interpreted with greater certainty than those achieved with traditional voltage waveform analyses. Moreover, the reference-independence of this analytical framework facilitates direct comparisons of results across laboratories; something that will require concerted coordination in the near-future.

The application of distributed source estimations (and statistical analyses thereof) further allowed Cappe et al. (2010) to localise early nonlinear effects to primary visual cortices, primary auditory cortices, as well as the posterior superior temporal sulcus (see also Raij et al. (2010) for MEG findings using a distributed inverse solution). These results resolve an ongoing debate regarding whether or not the early effects emanate from nominally visual (Fort et al., 2002a; Molholm et al., 2002) or nominally auditory cortices (Vidal et al., 2008) or both (Raij et al., 2010; Senkowski et al., 2007; Teder-Sälejärvi et al., 2002). Specifically, the findings of Cappe et al. and Raij et al. show there to be a widely distributed network of functionally coupled brain regions operating in concert during the time period of these early multisensory interactions. It has previously been suggested that early multisensory processes will focus in cortices associated with the less-efficient sensory modality. For example, an individual who is better at processing visual stimuli would show multisensory effects within auditory cortices and vice versa (Giard and Perronet, 1999). In contrast, the distributed network has been observed to be active during early stages of multisensory processing in a fashion independent of whether or not a given individual was more efficient in their behaviour with visual or auditory stimuli (Cappe et al., 2010, 2012).

What remains to be fully characterised is the finer temporal dynamics of early multisensory integrative effects. Because source estimations were performed after first averaging across time, Cappe et al. (2010) could not reveal if effects within their distributed network actually had distinct time courses such that activation within one region led that of the others. By contrast, Raij et al. (2010) used a more refined approach and estimated distributed sources on a millisecond-by-millisecond scale. Auditory responses within primary visual cortices onset at ∼53 ms, and visual responses within primary auditory cortices onset at ∼75–82 ms post-stimulus. Non-linear multisensory interactions began at approximately the same latency as the responses to the cross-modal inputs (cf. Table 4 in Raij et al. (2010)), suggesting that pathways for convergence may be the same as those generating interaction effects (although this remains to be more thoroughly examined; reviewed in Meredith et al. (2009) and van Atteveldt et al. (2014a)). In agreement with this notion are data from animals demonstrating auditory as well as somatosensory cross-modal convergence within the visual cortex of monkeys (Schroeder and Foxe, 2002; Wang et al., 2008), cats (Murata et al., 1965; Spinelli et al., 1968; Morrell, 1972; Majkowski and Sobieszek, 1972; Fishman and Michael, 1973), and mice (Iurilli et al., 2012). For example, Iurilli et al. (2012) showed that auditory inputs suppressed visual responses within infragranular layers of primary visual cortex via GABAergic synapses and moreover that this suppression was directly linked to performance (as measured by a conditioned motor response). These authors suggested that auditory inputs degrade the perception of the visual stimulus; something that will need to be reconciled with the many studies showing multisensory and cross-modal enhancement of

perception and behaviour (a sampling of which we review here). More generally, the work of Iurilli et al. (2012) constitutes an important step in not only characterising the neural bases of multisensory processes across circuit and synaptic levels, but also in linking physiology with behaviour. That said, however, few studies have characterised non-linear neural response interactions in the visual cortex of animals; something that will undoubtedly change in the coming years alongside improvements in recording techniques in awake, behaving animals as well as techniques for simultaneous recordings from multiple brain sites (e.g. Pigarev et al., 2009; Lanz et al., 2013; Gindrat et al., 2015).

The overall pattern observed in EEG/MEG studies in humans is suggestive of a network that may achieve its dynamic coupling through oscillatory activity. There is growing evidence that oscillations along with cross-frequency coupling may be particularly important in understanding some of the mechanistic bases of multisensory interactions as well as their link to behavioural outcome (e.g. van Atteveldt et al., 2014a; Gleiss and Kayser, 2014a, b; Mercier et al., 2013; Schepers et al., 2013, 2014; see also Lakatos et al., 2007, 2008). By way of two recent examples, Romei et al., (2012) found that a single beep can phase-align alpha oscillations to the sound within the occipital pole, and Cecere et al. (2015) used EEG together with tACS to show there is a tight link between an individual's alpha frequency and the temporal window of the flash-beep illusion (Shams et al., 2000) as well as between alpha power and the proneness to the illusion.

6. Brain stimulation (TMS/tACS)

Brain stimulation methods are a particularly effective means for drawing causal inference between brain activity and behaviour. Because the timing of stimulation can be finely controlled, one can also track the dynamics of these processes with a resolution on par with EEG/MEG. Likewise, brain stimulation methods can allow the experimenter to assay the excitability of the primary visual cortex and other early sensory areas and their modulation by information from other sensory systems. As will be detailed below, this is most readily achieved with phosphene induction. A full review of TMS as a methodology can be found in works by Pascual-Leone et al. (Pascual-Leone et al., 2000, 2002). In what follows, we summarise evidence from brain stimulation studies that demonstrate a causal role of multisensory processes within the primary visual cortex.

Phosphenes are the perceived sensation of flashes of light in the absence of visual stimulation following occipital TMS, and are believed to be generated by an activation current that is induced by the magnetic field of the TMS pulse (e.g., Allen et al., 2007; Moliadze et al., 2003). Phosphenes generated by stimulation of low-level visual areas (V1/V2) are typically perceived as brief, static sensations along the horizontal meridian or in the lower quadrant of the hemifield contralateral to the stimulated hemisphere. There is considerable inter-individual and inter-trial variability in the presence as well as the nature and strength of phosphenes, which may stem from anatomical/morphological differences as well as state-dependant effects (Silvanto and Pascual-Leone, 2008; Romei et al., 2008a). Nonetheless, there are now standard procedures for establishing the minimum intensity of occipital TMS required to elicit phosphenes (i.e., phosphene threshold or PT) (see, e.g., Pascual-Leone and Walsh, 2001; Ramos-Estebanez et al., 2007; Romei et al., 2007, 2008a,b, 2009).

Several independent laboratories have now demonstrated that non-visual stimuli enhance the excitability of low-level visual cortices within the occipital pole (Bolognini et al., 2010; Ramos-Estebanez et al., 2007; Romei et al., 2007, 2009; 2012; 2013; Spierer et al., 2013; see also Leo et al. (2011); Cecere et al. (2014)). In these studies, the experimenters first identified the PT for each

participant and then set the TMS intensity at a level below this PT value so that, under baseline conditions, phosphenes were reported on roughly 30–40% of trials. The core finding is that the likelihood of perceiving a phosphene dramatically increased when this same TMS pulse was paired with a sound (Fig. 2, right). Numerous control experiments have ruled out an explanation in terms of general attention or alerting (e.g. Romei et al., 2007, 2009; Spierer et al., 2013). Examination of the temporal dynamics of this excitability enhancement show on the one hand that it occurs during early stages after sound onset (Romei et al., 2007), even at pre-perceptual stages (Romei et al., 2009), and that the effects depend on the pre-stimulus alpha phase of visual cortices (Romei et al., 2012). Moreover, the effects persist in time, again following an alpha oscillation, and the persistence extends beyond sound offset (Romei et al., 2013). It is only during these extended time periods, however, that inter-individual differences in attentional preference on an independent task for the auditory or visual modality seem to play a role (Romei et al., 2013). Most critically, this brain stimulation evidence also supports a direct role of visual cortices in behavioural responses to sounds. Reaction times to sounds are facilitated by single-pulse TMS to the occipital pole, and the magnitude of this facilitation is comparable to and in fact correlates with that observed with veridical multisensory stimuli (Romei et al., 2007). In a similar manner, the latency at which the excitability of visual cortices is differentially enhanced by looming versus stationary sounds preceded and positively correlated with the duration required for an individual to reliability discriminate these sounds (Romei et al., 2009). In other words, the visual cortex seems to "know" the nature of the sound prior to an individual being aware of it. Finally, tuning of visual cortex activity to an external alpha oscillator via tACS stimulation causally modulates the temporal window of audio-visual integration shown to be responsible for the flash-beep illusion phenomenon (Cecere et al., 2015).

7. Discussion

The above studies provide convergent evidence that human primary visual cortex is a locus of multisensory processing. This was demonstrated at both anatomical (or at least fibre tracking) and functional levels. Moreover, there is reliable evidence that effects within the primary visual cortex directly impact behavioural outcome (at least for certain tasks). In parallel, the works reviewed here demonstrate how multisensory phenomena can be studied non-invasively and, more importantly, quantitatively assessed by taking advantage of particular strengths of each technique as well as advances in signal analyses.

Several general conclusions about multisensory processes in the primary visual cortex of humans are supported relatively solidly. First, there is both convergence and integration occurring within the primary visual cortex. This localisation is supported by all of the brain mapping methods reviewed above: diffusion-based as well as functional MRI measures, electrical neuroimaging of ERPs, EEG oscillations, single-pulse TMS and tACS over the occipital pole. While this review focused on the primary visual cortex, we would hasten to note that a similar conclusion regarding convergence and integration would apply as well to low-level (near primary) auditory cortex of humans, which most likely works in concert with regions such as the superior temporal sulcus to orchestrate many multisensory processes. Second, the primary visual cortex is involved in multisensory processes during early post-stimulus stages, as revealed by ERP/ERFs as well as TMS. As reviewed by De Meo et al. (2015), the eMSI have been observed across a wide variety of populations, experimental paradigms and task demands. Third, multisensory effects in the primary visual

cortex directly relate to behaviour and perception, as revealed by correlational (EEG/ERPs/ERFs) as well as more causal measures (TMS/tACS).

Collectively, these results are consistent with the emerging view that multisensory processes in the primary visual cortex, exemplified by the eMSI, constitute a hallmark of bottom-up multisensory processes that occur and affect behaviour in a fashion that is (largely) independent of the observer's goals (Matusz and Eimer, 2011) as well as the context in which stimuli are presented (ten Oever et al., 2015). One possibility is that the eMSI constitute a mechanism by which the brain can differentiate potentially important external events at a sufficiently early stage of stimulus processing, which may be advantageous at later stages between sensation and behaviour. The studies reviewed here converge to provide an important source of support for this perspective. On the one hand, the eMSI are observed in response to detection of multisensory stimuli that are devoid of established links between them, while also being modulated by such factors as the perceived looming/receding nature of the stimuli. On the other hand, higher-level factors, such as semantic congruence, seem ineffective in modulating multisensory processes in the primary visual cortex (Fort et al., 2002b; Molholm et al., 2004; Yuval-Greenberg and Deouell, 2007).

While we focused here on the correspondences of findings across diverse methods, the precise neurophysiologic mechanisms that underlie multisensory processes remain largely unknown. Some candidate mechanisms whereby cross-modal inputs could act include: (1) driving of visual responses (2) sub-threshold modulation, and (3) resetting of the phase of spontaneous ongoing activity (reviewed in van Atteveldt et al. (2014a); see also Cecere et al., 2015). Shedding light onto the relative contributions of these mechanisms is a domain of current research, which is complicated by the fact that the neural bases of non-invasive brain measures (and by extension their correspondence across methods) remain largely unresolved. For example, further studies will be required to relate changes in BOLD dynamics to nonlinear interactions evident in ERPs on the one hand and to changes in phosphene thresholds within visual cortex on the other. Some significant efforts in this direction are revealing that (i) the changes in visual cortex excitability (as indexed by phosphene induction) are directly related to pre-stimulus alpha phase over the occipital scalp (Romei et al., 2012); (ii) that proneness to the flash-beep illusion is related to inter-individual differences in baseline visual cortex excitability as indexed by occipital alpha power (Cecere et al., 2015; c.f. Romei et al. (2008b) for a direct link between phosphene perception and alpha power) as well as inter-individual differences in the primary visual cortex grey matter volume (de Haas et al., 2012); and (iii) individual alpha frequency over occipital areas is likely to set the temporal pace of multisensory binding (Cecere et al., 2015). More generally, though, drawing direct links between single-unit activity and BOLD/ERP etc. responses is not forcibly straightforward, and phenomena at the synaptic level might not be a direct translation of those at the single-unit level (we would defer the interested reader to Panzeri et al. (2015) for a recent treatment of this issue). This issue of linking single-unit and brain imaging measures is of tremendous importance not only from an analytical standpoint, but also with regard to extrapolating classical rules of multisensory interactions based on single-unit recordings (e.g. Stein and Meredith, 1993) to measurements in humans (and increasingly other species) based on brain imaging data (Stevenson et al., 2014).

Such is not to suggest that stimuli in realistic settings would not also be subjected to multisensory processes that are top-down in nature, such as those related to matching current goals and/or long-term memory (Matusz and Eimer, 2013; Matusz et al., 2015b). Some evidence in this direction is provided by studies of cross-modal selective attention that have focused on cross-frequency coupling as a potential neural mechanism (e.g. Zion-Golumbic et al., 2013 for evidence concerning auditory cortex; Lakatos et al., 2009 for evidence from non-human primates concerning visual cortex).

In summary, evidence from a full pallet of human brain imaging and brain mapping methods clearly demonstrates that multisensory processes occur within the human primary visual cortex. What is more, these processes can directly impact behavioural outcome. While the provocative claim of Ghazanfar and Schroeder (2006) that the whole of neocortex is multisensory in function has yet to be demonstrated, this can now be considered established in the case of the human primary visual cortex.

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