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Neuroplasticity and Crossmodal Connectivity in the Normal, Healthy Brain

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Neuroplasticity and Crossmodal Connectivity in the Normal, Healthy Brain

Objective: Neuroplasticity enables the brain to establish new crossmodal connections or reorganize old connections which are essential to perceiving a multisensorial world. The intent of this review is to identify and summarize the current developments in neuroplasticity and crossmodal connectivity, and deepen understanding of how crossmodal connectivity develops in the normal, healthy brain, highlighting novel perspectives about the principles that guide this connectivity.

Methods: To the above end, a narrative review is carried out. The data documented in prior relevant studies in neuroscience, psychology and other related fields available in a wide range of prominent electronic databases are critically assessed, synthesized, interpreted with qualitative rather than quantitative elements, and linked together to form new propositions and hypotheses about neuroplasticity and crossmodal connectivity.

Results: Three major themes are identified. First, it appears that neuroplasticity operates by following eight fundamental principles and crossmodal integration operates by following three principles. Second, two different forms of crossmodal connectivity, namely *direct crossmodal connectivity* and *indirect crossmodal connectivity,* are suggested to operate in both unisensory and multisensory perception. Third, three principles possibly guide the development of crossmodal connectivity into adulthood. These are labeled as the *principle of innate crossmodality*, the *principle of evolution-driven 'neuromodular' reorganization* and the *principle of multimodal experience*. These principles are combined to develop a three-factor interaction model of crossmodal connectivity.

Conclusions: The hypothesized principles and the proposed model together advance understanding of neuroplasticity, the nature of crossmodal connectivity, and how such connectivity develops in the normal, healthy brain.

Keywords: Neuroplasticity; crossmodal connectivity; innate crossmodality; evolution-driven crossmodality; multimodal experience

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Public Significance

Neuroplasticity and crossmodal connectivity are essential to sensing and perceiving a multisensorial world. These two intertwined processes allow individuals to learn from and adapt to altered sensory environments. The principles of crossmodal connectivity suggested in this review, and the proposed model built on these principles, advance understanding of the origins of crossmodal connectivity in the normal, healthy brain.

Recent years have witnessed an explosion of interest in neuroplasticity, the capacity of the brain to change its anatomical and functional architecture due to changes in sensory input or experience. These changes can occur on a variety of levels, ranging from cellular changes involved in learning to large-scale changes involved in cortical remapping, in response to brain injury and disease (Bola, Zimmermann et al., 2017; Dayan & Cohen, 2011; Nudo, 2013; Siuda-Krzywicka et al., 2016). Neuroplasticity enables the brain to rearrange synaptic connections or form new connections between neurons, allowing individuals to learn, adapt to altered sensory environments or sensory deprivation (Green & Bavelier, 2008; Heimler, Striem-Amit, & Amedi, 2015), and empower patients to recover from brain injury and brain damage (Finger & Almli, 1985).

Sensory deprivation or injury induces large-scale reorganization of information-processing areas in the brain (Hirsch, Corinna, & Merabet, 2015; Lomber, Meredith, & Kral, 2011; Merabet & Pascual-Leone, 2010; Pavani & Roeder, 2012). In addition to the adaptive and compensatory neuroplasticity due to sensory deprivation (Bavelier & Neville, 2002; Meredith, Kryklywy et al., 2011; Pascual-Leone, Amedi, Fregni, & Merabet, 2005; Rauschecker, 1995), training or relevant experience can also induce neuroplasticity in sensory-deprived individuals, as in the blind (e.g., Likova, 2012, 2014, 2015, 2017, 2018; Pavani & Roeder, 2012). Research has shown that training- or experience-driven neuroplasticity can operate within the limits of sensory divisions (Pavani & Roeder, 2012) as well as beyond the limits of sensory divisions (Likova, 2015, 2017, 2018). These changes that go beyond sensory divisions exemplify crossmodal connectivity, where such functional changes are either multi-modal or modality-independent. Sensory divisions of the brain comprise cortical areas, including primary sensory cortices (e.g., primary visual, auditory and somatosensory cortices) and lower-order sensory association cortices (e.g., secondary auditory association areas, visual association areas) that are specialized for sensory functions. Sensory divisions, by this definition, exclude the tertiary association or higher-order integrative cortices not directly associated with a particular sense (e.g., prefrontal cortex, superior temporal sulcus, intraparietal complex; Ghazanfar & Schroeder, 2006; Jung, Cloutman, Binney, & Ralph, 2017), and the limbic and subcortical regions (e.g., amygdala, hippocampus, superior colliculus, inferior colliculus; Budinger, Laszcz, Lison, Scheich, & Ohl, 2008; Yang, Lee, & Kim, 2020). Research has shown that within the limits of sensory divisions visual cortex typically processes visual inputs and responds to visual training, somatosensory cortex processes tactile inputs and responds to tactile training, and so on (Pavani & Roeder, 2012). Neuroplasticity beyond the limits of sensory divisions has been exemplified in a series of studies in the blind (Likova, 2015, 2017, 2018). Specifically, these studies have demonstrated that the hippocampus and the temporal pole undergo dramatic and remarkable reorganization during cognitive functioning, such as during memory-guided drawing based on a haptic form of visual art drawing in the blind (Likova, 2015, 2017, 2018). However, sensory deprivation or brain injury is not necessary for demonstrating neuroplasticity. In fact, the human brain is constantly adapting to environmental inputs and experiences throughout the life span. There is a wealth of evidence that neuroplasticity occurs in the normal, healthy brain due to training or experience (Bola, Siuda-Krzywicka et al., 2017; Nudo, 2013; Siuda-Krzywicka et al., 2016; Ujiie, Yamashita, Fujisaki, Kanazawa, & Yamaguchi, 2018), and that experience-dependent changes in the brain are reflected in behavioral and cognitive changes (Kandel, 2000). Neuroplasticity enables the brain to establish new crossmodal networks or reorganize existing networks that are essential to sensing and perceiving a multisensorial world. The intent of this review is to identify and summarize the current developments in neuroplasticity and crossmodal connectivity and deepen understanding of how crossmodal connectivity develops in the normal, healthy brain, highlighting novel perspectives about the principles that guide this connectivity.

To this end, the relevant studies on neuroplasticity and crossmodal connectivity in the normal, healthy brain are analyzed, synthesized, and interpreted, linking the findings together toward new propositions or hypotheses about these processes. As part of this broad goal, the studies in psychology and neuroscience investigating the principles of neuroplasticity and crossmodal integration are briefly revisited, followed by an appraisal of the studies investigating crossmodal connectivity in both unisensory and multisensory perception, and the developmental aspects and origins of such connectivity from a variety of novel perspectives. A narrative review is chosen as the interpretative methodology in order to capture the varied literature in this wide-ranging field of investigation.

Methods

In this narrative review, two broad neurobehavioral topics were addressed: (i) neuroplasticity and multisensory processing, and (ii) crossmodal connectivity in the normal, healthy brain. To accumulate the most relevant articles for each of these neurobehavioral topics or aspects, a wide range of electronic databases, including PubMed, Scopus, PsychInfo, MEDLINE, ScienceDirect, Google Scholar, and Web of Science were searched. The key terms used in this search were: neuroplasticity, principles of neuroplasticity, multisensory or crossmodal integration, principles of multisensory or crossmodal processing, crossmodal neuroplasticity, crossmodal connectivity or network, anatomical basis for crossmodal connectivity or network, development of crossmodal connectivity, origins of crossmodal connectivity, innateness of crossmodality, evolution-driven crossmodality; and multimodal or multisensory experience. To maximize the likelihood that all relevant studies were identified, electronic database searching was supplemented by examining the reference list of relevant retrieved articles. In addition to peer-reviewed journal articles (both empirical and theoretical/review), books and gray literature (e.g., unpublished studies, reports, dissertations, conference papers and abstracts) were also explored to identify more references to published works that the database search might have missed.

Because it was a narrative review, no predefined criteria or protocols were set for the database search. However, after the unstructured search, articles were read and assessed for relevance. Neuroimaging and behavioral studies were considered for inclusion only if they enrolled normal human or nonhuman animal subjects and were relevant to the topics of interests. Nonhuman animal studies were included as much of the current knowledge about the above topics comes from studies in model animals that can provide further insight into mechanisms that may not be ethical to directly measurable in humans. Studies that focused on neurological or neurocognitive disorders and treatments or rehabilitation were not included as they are beyond the scope of this review. Studies that assessed neuroplasticity and crossmodality in sensory deprived populations such as blind, deaf, and other atypically developed humans or animals were mostly excluded, with the exception of a few that were necessarily included for conceptualizing the topics of interests.

Thus after screening through the retrieved articles and materials, a total of 344 peer-reviewed articles and book chapters or grey outlets published in English during the period of 1929 to 2020 were deemed relevant and included in the review. All articles and book chapters were reviewed and analyzed by the first author of this review that started in July 2018 and continued as needed until the write-up of this work. Received results were checked for accuracy and relevance by the other contributing authors, and discrepancies, if occurred, were resolved through discussion and consensus. The articles and book chapters were examined in light of the current understanding of the psychological and neurobiological processes that underlie neuroplasticity and development of crossmodal connectivity in the normal, healthy brain. Due to the narrative nature of this review, results are critically assessed, summarized, synthesized, and discussed by description and exploration with qualitative elements rather than with quantitative elements that is usually done in a systematic review following a set of predefined guiding questions or objectives.

Results

The selected studies were categorized and analyzed according to the aforementioned topics of interests. Three major themes were identified, one under the first topic and two under the second topic. These themes are: (i) neuroplasticity and multisensory processing which covers the principles of neuroplasticity and the principles of multisensory integration, (ii) crossmodal connectivity in the normal, healthy brain which covers crossmodal effects, crossmodal connectivity in unisensory and multisensory perception and anatomical basis for crossmodal connectivity, and (iii) development of crossmodal connectivity in the normal, healthy brain explained by a novel model of crossmodal connectivity development that combines three principles of crossmodal connectivity development, namely *the principle of innate crossmodality*, *the principle of evolution-driven 'neuromodular' reorganization* and *the principle of multimodal experience*.

Neuroplasticity and multisensory processing

Multisensory processing encompasses all the various ways in which the presence of information in one sensory modality can adaptively influence the processing of information in a different modality (Briscoe, 2016). Multisensory processing has a family of functions rather than a single operation (Meijer, Mertens, Pennartz, Olcese, & Lansink, 2019). One such function is multisensory (crossmodal) integration, defined as the process by which the brain synthesizes and unifies two or more different sensory signals, and is key to achieving a stable and coherent percept of the external world (Bizley, Maddox, & Lee, 2016; Maddox et al., 2015; Paraskevopoulos & Herholz, 2013; Stein, Perrault, Stanford, & Rowland, 2009; Yau, DeAngelis, & Angelaki, 2015). Research has shown that multisensory integration is plastic or adaptive to experience (Stein & Rowland, 2011), and strongly interacts with neuroplasticity of the human brain (Paraskevopoulos & Herholz, 2013). On the one hand, experience and training in various domains modify how information from different sensory modalities is integrated, and on the other hand, multisensory training paradigms seem to be particularly effective in driving functional and structural plasticity of the brain (Paraskevopoulos & Herholz, 2013). Research has shown that these two interactive processes operate following distinct sets of principles as outlined below.

Principles of neuroplasticity. The developing normal brain shows a remarkable capacity for neuroplastic changes in response to a wide range of sensory and motor experiences (Kolb, Mychasiuk, Muhammad, & Gibb, 2013). The pioneering works of Kleim and Jones (2007), and Kolb and Gibb (2008) suggest that the experience-dependent neuroplastic changes follow a set of basic principles (summarized in Table 1). There are some variations and similarities between the principles suggested by these authors, which overlap between such concepts as 'use it or lose it' and 'use it and improve it' that are discussed here; though some of their arguments about fine differences between training and repetition are omitted for brevity. As outlined in Table 1, the first principle 'use it and improve it, or lose it' states that training that drives a specific brain function or actively engages neural circuits can lead to functional enhancement, and a failure to drive or engage it for an extended period of time can lead to functional degradation. The second principle, the principle of 'sufficiency of training or repetition,' states that induction of plasticity requires sufficient training or repetition. Thus in order to gain mastery of a newly learned or relearned skill or behavior repetition of that skill or behavior is necessary as to induce lasting neural changes for that mastery to occur. The third principle, the principle of 'salience of experience,' states that the training experience must be sufficiently salient to induce plasticity as mere engagement of a neural circuit in task performance is not sufficient to drive plasticity. The fourth principle, the principle of 'time-dependence,' states that the nature of plastic changes (e.g., stability) observed after training and its behavioral relevance depend on when one looks at the brain. The fifth principle, the principle of 'age-dependence,' states that the training-induced plasticity occurs more readily in younger brains than older brains. The sixth principle, the principle of 'transference,' states that plasticity within a set of neural circuits has the ability to promote concurrent or subsequent plasticity. Thus, plasticity in response to one training experience can enhance the acquisition of similar behaviors. The seventh principle, the principle of 'interference,' states that plasticity within a given neural circuitry has the ability to impede the induction of a new, or expression of an existing, plasticity within the same circuitry. Thus, plasticity in response to one experience can interfere with new learning, the acquisition of other behaviors. The final principle, the principle of 'task-specificity', states that neuroplasticity operates in a task-specific manner. For example, rats trained on a visuospatial task show specific changes in visual cortex whereas rats trained on motor tasks show specific changes in motor cortex (e.g., Greenough & Chang, 1989; Kolb, Cioe, & Comeau, 2008; Withers & Greenough, 1989).

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Task-specific neuroplasticity has been widely investigated in the last decade or so, suggesting that it is not unique to the visual or motor cortex. Rather, it can operate in other sensory cortices, including the auditory, not only intramodally but crossmodally as well (Amedi, Hofstetter et al., 2017; Bola, Zimmermann et al., 2017; Likova, 2012). The process of plasticity occurring within a single sensory modality is referred to as intramodal or unisensorial plasticity. Crossmodal neuroplasticity can be defined as the adaptive reorganization of neurons to integrate the functions of two or more sensory modalities. Prior studies have demonstrated that task-specific crossmodal neuroplasticity occurs not only in sensory deprived population but in the normal (healthy sighted or hearing) population as well (e.g., Collignon et al., 2011; MacSweeney et al., 2002; Merabet, Thut et al., 2004; Pascual-Leone & Hamilton, 2001; Ricciardi, Handjaras, & Pietrini, 2014). Thus, task-specific neuroplasticity is probably a general principle in the brain (Amedi, Hofstetter et al., 2017; Bola, Zimmermann et al., 2017; but see also Lewis, Saenz, & Fine (2010) who failed to show task-specificity in crossmodal neuroplasticity). According to a review, task-specific crossmodal (modality-independent) activation can be considered as *supramodal* responses of the brain to a perceptual input or task that occur independently of the sensory modality feeding that input to the brain (Heimler et al., 2015). That review further suggested that a combination of the connectivity bias and sensitivity to task-distinctive features might account for task-specific crossmodal neuroplasticity in the sensory cortices as a whole, from the higher-order occipital or temporal cortices to the primary sensory cortices. The connectivity bias states that task-specific recruitment draws on pre-existing cortical connections linking the sensory cortices, such as occipital and temporal cortices, and task-distinctive feature sensitivity posits that task-specific recruitment can emerge from the intrinsic circuitry of the sensory cortices in a much more general way (Heimler et al., 2015).

Principles of multisensory integration. Due to its neural and behavioral advantages (Alvarado, Vaughan, Stanford, & Stein, 2007, Miller, Stein, & Rowland, 2017, Murray, Eardley et al., 2018), research in psychology and neuroscience has given much more attention than ever before to understanding the principles of multisensory/crossmodal integration and candidate neural mechanisms (Stein, Stanford, & Rowland, 2014). Thus far, based on neuronal recordings in the superior colliculus (SC, a brainstem structure) of cats three general principles or 'rules of thumb' have been suggested for the operation of crossmodal integration (Otto, Dassy, & Mamassian, 2013; Stein, Stanford, & Rowland, 2014). These principles are listed in Table 2.

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The first principle, the principle of temporal coincidence, posits that the sensitivity of neurons to multisensory inputs is dependent on their relative timing (Hebb, 1949; Otto et al., 2013; Stein & Wallace 1996; Stein, Stanford, & Rowland, 2014). Sensory inputs that are presented in close temporal proximity enhance response magnitude of multisensory neurons and are likely to be integrated, whereas sensory inputs that are far apart in time elicit each corresponding unisensory responses (Kadunce, Vaughan, Wallace, & Stein, 2001; Meredith, Nemitz, & Stein, 1987). A second principle, the principle of spatial proximity, states that sensory inputs that are in spatial proximity produce multisensory enhancement and are likely to be integrated, whereas sensory inputs that are spatially far apart may cause response inhibition (Kadunce et al., 2001; Meredith, Nemitz et al., 1987; Otto et al., 2013; Stein & Meredith, 1993; Stein, Stanford, & Rowland, 2014). The two sensory inputs are said to be in spatial proximity if both fall within the receptive field (RF) of the same multisensory neuron (Cuppini, Magosso, & Ursino, 2011) or within the overlap of the RFs of different sensory modalities (Stein, 1998). A third principle, the principle of inverse effectiveness, suggests that the magnitude of multisensory integration depends on the efficacy of the sensory inputs being integrated (Stein, Stanford, Ramachandran, Perrault, & Rowland, 2009). It has been argued that two sensory inputs presented simultaneously elicit multisensory neural response that exceeds either unisensory neural response produced by those inputs if presented separately (Alvarado, Stanford, Rowland, Vaughan, & Stein, 2009; Gondan, Niederhaus, Rösler, Roede, 2005; Meredith & Stein 1986; Otto et al., 2013; Perrault, Vaughan, Stein, & Wallace, 2003; Stanford & Stein 2007; Stanford, Quessy, & Stein, 2005; Stein & Wallace 1996). This principle appears to suggest a link between neuronal activity and behavioral benefits of sensory integration (Kayser & Logothetis, 2007). At the behavioral level, the computational benefit of synthesizing inputs from different senses is optimum when each sense alone provides little information about the external world (Kayser & Logothetis, 2007; Stein, Stanford, & Rowland, 2014). Then, assuming that stronger responses also convey more information about the stimulus, this translates to a stronger response enhancement in the case of weak neuronal responses (Kayser & Logothetis, 2007).

Crossmodal connectivity in the normal, healthy brain

Despite substantial progress in the understanding of the principles of neuroplasticity and the principles of crossmodal or multisensory integration, little interest has been shown thus far to the understanding of *crossmodal connectivity* in the brain of people who experience typical sensory development. The concept of *crossmodal connectivity* is closely related to but sharply distinct from the concept of *crossmodal integration*. *Crossmodal integration* is the process of consolidating input signals from simultaneously experienced multiple senses, such as visual and tactile senses, to form a rich and coherent percept of the environmental objects or events (Bizley, Maddox et al, 2016; Gharaei, Arabzadeh, & Solomon, 2018; Maddox et al., 2015; Stein, Stanford, & Rowland, 2014; Tsilionis & Vatakis, 2016) whereas *crossmodal connectivity* which allows crossmodal integration to operate can be defined as how different sensory modalities are functionally connected to each other (Parise, 2016), how activity in different sensory regions or cortices can covary in response to stimulation over time (Hagmann et al., 2008), or how stimulation in one sensory modality influences the functional or anatomical architecture of a different sensory modality (Chen, Puschmann, & Debener, 2017; Laing, Rees, & Vuong, 2015; Sung & Ogawa, 2013; Yau, DeAngelis et al., 2015). Thus, *crossmodal connectivity* is a predisposition (innate, evolved, or pragmatically/naturally learned) of the sensory modalities including their ability to activate each other during information processing whereas *crossmodal integration* is the outcome resulting from such predisposition in appropriate time and stimulus setting (see Table 2). However, there is much uncertainty about the nature of crossmodal connectivity underlying crossmodal integration. Thus, it is poorly understood how different sensory modalities or cortices develop cooperative and functional networks with one another to be effective in processing and integrating multisensory information. To fill this gap, the known patterns of crossmodal connectivity between the major sensory (visual, tactile and auditory) cortices in the normal, healthy brain, and their anatomical basis are critically discussed below.

Crossmodal effects. Sensory systems do not work in isolation. Therefore, crossmodal effects occur when experience or stimulation in one sensory modality, such as the visual modality, recruits cortical resources of another sensory modality, such as auditory or tactile modality. Crossmodal effects have been widely studied in both unisensory and multisensory perception. The findings of those studies have unequivocally demonstrated that crossmodal effects occur not only in sensory deprivation but in the normal, healthy brain as well (e.g., Amedi, Stern et al., 2007; Foxe et al., 2002; Fu et al., 2003; Haslinger et al., 2005; Lemus, Hernández, Luna, Zainos, Romo, 2010; Martuzzi et al., 2007; Pekkola, Ojanen, Autti, Jaaskelainen, Mottonen, Tarkiainen et al., 2005;

Pekkola, Ojanen, Autti, Jaaskelainen, Mottonen, Sams, 2006; Schürmann, Caetano, Hlushchuk, Jousmäki, & Hari, 2006; Siuda-Krzywicka et al., 2016). An in-depth review of the findings of studies in humans and model animals from a range of species on neuroplasticity and crossmodality suggests that crossmodal effects of sensory stimulation can occur in the normal, healthy brain through two different types of neural connections, namely *direct crossmodal connectivity* and *indirect crossmodal connectivity*, operating in both unisensory and multisensory perception. The *indirect connectivity* likely operates via a sensory (primary or lower-order association) or a nonsensory (higher-order cortical or subcortical) intervening zone (which facilitates crossmodal interactions or integrates crossmodal signals) whereas *direct connectivity* does not involve any intervening/ integration zone of this type.

Crossmodal connectivity in unisensory perception. A wealth of studies in unisensory perception has demonstrated that *crossmodal connectivity* likely operates when sensory cortices are activated in a task-specific manner by (unisensory) stimuli of other sensory modalities (Driver & Spence, 1998; Fu et al., 2003; Morrell, 1972; Petro, Paton, & Muckli, 2017). Thus, a sensory-specific modality that receives environmental stimuli sends input projections to and activates a sensory cortex (primary and/or secondary) specialized for processing stimuli of a second sensory modality (Figure 1a, b). In support of this, neuroimaging and electrocorticographic studies in human participants with normal or corrected-to-normal sight and normal hearing have demonstrated that in response to unisensory stimuli, crossmodal effects can occur not only within primary sensory cortices, but within secondary or association cortices as well. For example, visual stimuli evoke crossmodal effects in both primary auditory (Martuzzi et al., 2007; Raij et al., 2010) and adjacent auditory (Pekkola, Ojanen, Autti, Jaaskelainen, Mottonen, Tarkiainen et al., 2005; Pekkola, Ojanen, Autti, Jaaskelainen, Mottonen, Sams, 2006) cortices. Tactile stimuli evoke crossmodal effects in primary visual cortex (Merabet, Swisher et al., 2007; Zangaladze, Epstein, Grafton, & Sathian, 1999), primary auditory cortex (Nordmark, Pruszynski, & Johansson, 2012), secondary visual cortex (Nordmark et al., 2012) and auditory subregions (Nordmark et al., 2012; Schürmann et al., 2006) as well. Similarly, auditory stimulation in normal humans activates not only primary visual (Brang et al., 2015; Martuzzi et al., 2007; Mercier et al., 2013; Raij et al., 2010; Vetter, Smith, & Muckli, 2014) and primary somatosensory (Sugiyama, Takeuchi, Inui, Nishihara, & Shioiri, 2018) cortex, but somatosensory association regions as well (Pérez-Bellido, Anne Barnes, Crommett, Yau, 2018). Moreover, auditory attention, but not passive exposure to sounds, can routinely activate peripheral regions of visual cortex when participants attend to sound sources outside the visual field (Cate et al., 2009). In line with these human studies, single unit recordings, molecular mapping and neuroimaging studies in model animals have shown that neurons in the (primary) visual cortex can be driven by acoustic stimuli (Hirst, Khomami, Gharat, & Zangenehpour, 2012; Morrell, 1972), and neurons in the auditory cortex, such as core and caudomedial or belt auditory areas, can be driven by visual stimuli or scenes (Bizley, Nodal, Bajo, Nelken, & King, 2007; Kayser, Petkov, Augath et al., 2007).

It has been further demonstrated that tactile (Braille) reading recruits visual cortex, including the visual word form area, in sighted Braille readers (Siuda-Krzywicka et al., 2016), and professional pianists recruit auditory cortex for visuomotor processing – watching silent piano playing (Haslinger et al., 2005). Even more interestingly, sights of touching evoke activity in somatosensory cortex (Hansson et al., 2009), visual cues to an object's surface properties evoke activity in secondary somatosensory cortex (Sun, Welchman, Chang, & Luca, 2016), and the mere sight of photographs (Proverbio, D'Aniello, Adorni, & Zani, 2011), and lipreading (watching a speaker's lips during face-to-face conversation; Calvert et al., 1997) activate auditory cortex. These particular findings together suggest the role of crossmodal mental imagery, the formation of mental image in a sensory modality from the stimulation or experience in another sensory modality, in perception and neuroplasticity: what people imagine in their minds can affect how they perceive the world, and how the sensory cortex reorganizes in absence of actual stimulation (e.g., Berger & Ehrsson, 2018; Nanay, 2018; O'Dowd, Cooney, McGovern, & Newell, 2019; Schmidt & Blankenburg, 2019; Spence & Deroy, 2013; Wise, Frangos, & Komisaruk, 2016). However, perhaps mental imagery cannot be generated before relaying input signals from the first, stimulated sensory cortex on to the second, nonstimulated sensory cortex, such that the role of mental imagery that operates in a top-down manner does not preclude the process of crossmodal connectivity.

Here, it is important to note that the first cortical territories processing environmental inputs are classically-defined primary sensory cortices that receive modality-specific information through their primary afferent pathways (Petro et al., 2017; Teichert & Bolz, 2018). Indeed, the primary sensory cortices have both direct and indirect projections to other sensory cortices. For example, the primary auditory cortex (A1) has direct and indirect projections to the primary visual cortex (V1; Miller & Vogt, 1984; Cappe, Rouiller, & Barone, 2009). Thus the inputs received from the external world through the visual modality are first processed in its primary cortical territory wherefrom the input signals are dispatched to and processed in the primary cortical territory of the auditory modality (or vice versa) through direct connections between V1 and A1 (correspond to V and A modalities respectively; Figure 1a), or through indirect connections via a third intervening cortical zone (Figure 1b). It can be hypothesized that, in forming an indirecrt connectivity between V1 and A1, perhaps a relevant sensory association cortex, such as visual or auditory association cortex, plays the intervening role. Similarly, in forming an indirect connectivity between V1 and auditory association area perhaps A1 plays the intervening role, and in forming an indirect connectivity between A1 and visual association area perhaps V1 plays the intervening role. However, in any indirect crossmodal connections operating in unisensory perception, the intervening cortical zone likely facilitates the connectivity rather than integrating the unisensory stimulus.

Because of these crossmodal connections sensory cortices, particularly the primary sensory cortices do not work in isolation but are substantially affected by each other (Teichert & Bolz, 2018). On a neural level, these effects may be either excitatory or inhibitory (Stanford, Quessy et al., 2005). The excitatory effects accord well with the crossmodal effects of a stimulated sensory cortex on a nonstimulated sensory cortex (see above) whereas the inhibitory effects do not. Here, it can be proposed that whether a crossmodal effect on nonstimulated sensory cortex will be excitatory or inhibitory is determined by multiple factors. One potential factor is the stimulus context. In support of this, a study in mice demonstrated that the presentation of a high-amplitude sound stimulus results in hyperpolarization of the membrane potential of V1 neurons and somatosensory neurons (Iurilli et al., 2012). This crossmodal response suggests that V1 may adopt a different coding scheme depending on stimulus configuration (Meijer, Montijn, Pennartz, & Lansink, 2017). A more recent study has shown that A1 neurons projecting to V1 in awake mice preferentially respond to abrupt sounds, having a differential effect on V1 activity based on visual context: inhibitory in dark and excitatory in light condition (Deneux et al., 2019). This result further indicates how crossmodal inhibitory processes operating within traditional modality-specific cortices can be switched OFF or ON in different circumstances (Laurienti et al., 2002), allowing or impeding the operation of excitatory processes. However, a second possibility is that distinct neural circuits may mediate sound-induced excitatory and inhibitory influences on V1 (Meijer, Mertens, Pennartz, Olcese et al., 2019). One prior study using in vitro electrophysiological recordings demonstrated that excitatory influences were mediated by projections from Layer 5 in A1 to Layer 1 interneurons in V1, and these interneurons then further inhibited Layer 2–3 interneurons impinging on pyramidal cells, which might thus be disinhibited, resulting in enhanced visual responses (Ibrahim et al., 2016). The hyperpolarizing effect revealed in Iurilli et al.'s (2012) study was instead elicited by A1 Layer 5 projections onto Layer 5 pyramidal neurons in V1, and these were shown to enhance the activity of V1 interneurons, which then might mediate the reported sound-induced hyperpolarization (Meijer, Mertens, Pennartz, Olcese et al., 2019). It is therefore plausible that different neural circuits coexist between A1 and V1, and that the net effect of auditory influences on V1 is due to the combination of a number of stimulus parameters (e.g., volume, frequency, temporal pattern), all of which determine how these distinct neural circuits interact (Meijer, Mertens, Pennartz, Olcese et al., 2019). The above propositions might apply for crossmodality not only between visual and auditory cortices, but for crossmodality between other sensory cortices as well.

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Crossmodal connectivity in multisensory perception. An inspection of the available data in the literature on crossmodal neuroplasticity indicates that there are at least one *direct* and four *indirect crossmodal connectivities* operating in multisensory perception, such as in the perception of audiovisual stimuli (Figure 1c – g). Three of these connectivities likely operate within the limits of sensory divisions and the remaining two outside the limits of sensory divisions. Specifically, the direct crossmodal connectivity likely operates when simultaneously experienced stimuli from two sensory modalities converge and interact in a sensory cortex specialized for processing information of either of the two sensory modalities (Figure 1c). Two of the indirect crossmodal connectivities likely operate via a sensory zone not specialized for processing information of the connected sensory modalities, such as when simultaneously experienced stimuli from two sensory modalities converge and interact in a third primary sensory cortex (Figure 1d) or in a lower-order sensory association cortex (Figure 1e). A plethora of psychophysical and neuroimaging studies in humans and model animals provides intriguing evidence in support of these sorts of connections that are likely to form following the principles of crossmodal integration discussed earlier in this review (e.g., Otto et al., 2013; Stein, Stanford, & Rowland, 2014). Specifically, psychophysical studies in humans have shown that auditory sounds presented simultaneously with vibrotactile stimuli affect the perception of vibrotactile stimuli at the same or similar frequencies (Ro, Hsu, Yasar,, Elmore, & Beauchamp, 2009; Wilson, Reed, & Braida, 2010; Yau, Olenczak, Dammann, & Bensmaia, 2009), and conversely, somatosensory vibrations influence the perceived intensity of auditory stimuli (Yau, Weber, & Bensmaia, 2010), indicating crossmodal interactions between these two sensory modalities. Neuroimaging studies in humans have shown that visuo-tactile interactions occur in auditory cortex (King & Walker, 2012), primary somatosensory cortex (Dionne, Meehan, Legon, & Staines, 2010), and visual cortex (Amedi, Malach et al., 2001; Amedi, Jacobson, Hendler, Malach, & Zohary, 2002), including the dorsal part of the lateral occipital complex (Amedi, von Kriegstein, van Atteveldt, Beauchamp, & Naumer, 2005); audio-tactile interactions occur in auditory cortex (Kayser, Petkov, Augath et al., 2005; Murray, Molholm et al., 2005; Plöchl, Gaston, Mermagen, König, & Hairston, 2016; Wu, Stefanescu, Martel, & Shore, 2015), including the caudomedial auditory area (Foxe et al., 2002; Fu et al., 2003); and audio-visual interactions occur in both visual (Giard & Peronnet, 1999) and auditory cortices, including the primary (Martuzzi et al., 2007; Murray, Thelen et al., 2016; Noesselt, Rieger et al., 2007; Raij et al., 2010). All these findings have been corroborated by the findings of studies in model animals. For example, studies in monkeys and ferrets have revealed that audio-visual interactions occur in both visual (e.g., Wang, Celebrini, Trotter, Barone, 2008) and auditory cortices, including the core (primary) and belt auditory areas (Bizley, Nodal et al., 2007; Bizley & King, 2008; Ghazanfar, Maier, Hoffman, Logothetis, 2005; Kayser, Petkov, Augath et al., 2007; Kayser, Petkov, & Logothetis, 2008, 2009). Similar to audio-visual interactions, audio-tactile interactions occur in both the core (Lakatos, Chen, O'Connell, Mills, & Schroeder, 2007) and caudal lateral belt auditory areas (Kayser, Petkov, Augath et al., 2005). All these findings together suggest that crossmodal interactions operate in early sensory areas, including the primary sensory and lower-order sensory association areas (Carter, Chen, Lovell, Vickery, Morley, 2014; Kayser, 2010; Takagaki, Zhang, Wu, & Lippert, 2008; Teichert & Bolz, 2018; Vasconcelos et al., 2011), indicating that they comprise not only unisensory neurons but multisensory neurons as well (Driver & Spence, 2000). Thus, it is no longer accurate to functionally characterize any sensory cortices as truly unisensory, but rather multisensory with a unisensory specialization.

The remaining two crossmodal connectivities likely operate in multisensory perception via a few so-called nonsensory zones, such as when multisensory stimuli converge and interact in a higher-order multisensory area (Figure 1f) or in a multisensory subcortical structure (Figure 1g). Evidence in support of these connections operating outside the limits of sensory divisions also comes from research in both humans and model animals. For example, neuroimaging research in humans has shown that visuo-tactile interactions occur in perirhinal cortex, a multisensory area located in the medial temporal lobe (e.g., Holdstock, Hocking, Notley, Devlin, & Price, 2009), and both audio-visual and audio-tactile interactions occur in posterior STS, a crossmodal binding site in the temporal lobe (Amedi, von Kriegstein et al., 2005; Beauchamp, Lee, Argall, & Martin, 2004; Beauchamp, Yasar, Frye, & Ro, 2008). Through connectivity analyses an fMRI study in human participants has shown that audio-visual correspondence in temporal pattern induces feedback influences from the STS upon primary visual and primary auditory areas but not vice versa (Noesselt, Rieger et al., 2007). Nonhuman primate studies suggest that the STS not only receives converging audio-visual inputs (Barraclough, Xiao, Baker, Oram, & Perrett, 2005; Kayser, Petkov, Augath et al., 2007), but is thought to integrate them as well (Benevento, Fallon, Davis, & Rezak, 1977; Bruce, Desimone, & Gross, 1981). Research in model animals has further demonstrated that integrations of bisensory stimuli can occur in the higher-order cortical areas, such as the frontal cortex (PFC), the ventrolateral PFC, and in the subcortical structures as well. For example, nonhuman primate studies have demonstrated audio-visual (voice – face) interactions in the PFC (Fuster, Bodner, & Kroger, 2000), particularly in the ventrolateral PFC (Sugihara, Diltz, Averbeck, & Romanski, 2006). Studies in rodents have demonstrated that the posterior parietal cortex (PPC), a higher-order multimodal association area (Lynch, 1980), that has connections with the PFC (Hovde, Gianatti, Witter, & Whitlock, 2018; Olsen et al., 2019) can be activated by stimulus detection task in audio-visual conflicts (Song et al., 2017). About the role of subcortical zones, a few pioneering studies on multisensory processing have shown that visuo-tactile interactions occur in rat SC (Gharaei et al., 2018), audio-visual integrations occur in cat SC (Peck, 1987) and in guinea-pig SC (King & Palmer, 1985), and audio-tactile integrations occur in rat/mouse inferior colliculus (IC; Casseday, Fremouw, & Covey, 2002; Lesicko, Hristova, Maigler, & Llano, 2016; Szczepaniak & Møller, 1993; Yang et al., 2020; Winer & Schriner, 2005; Wu et al., 2015).

The above discussion on crossmodal connectivity exclusively focuses on bimodal interactions; however, there is intriguing evidence that more than two modalities can also interact in the perception of a multisensorial world (the complex connections underlying such interactions are not shown here schematically). For example, research in normal humans has demonstrated trimodal interactions between visual, vestibular and tactile modalities (Kaliuzhna, Ferrè, Herbelin, Blanke & Haggard, 2016), and between auditory, visual, and tactile modalities (Diederich & Colonius, 2004; Hagmann & Russo, 2016; Kassuba et al., 2011; Pomper et al., 2014; Wozny, Beierholm & Shams, 2008). A few studies in model animals have demonstrated that trimodal interactions between visual, auditory, and somatosensory modalities occur in the deep layers of the SC (Ghose, Maier, Nidiffer & Wallace, 2014; Wallace, Meredith, & Stein, 1998) or in the left fusiform gyrus (Kassuba et al., 2011). However, it merits further investigation to see whether trimodal interactions also occur in unimodal zones of the cerebral cortex.

Anatomical basis for crossmodal connectivity. Research in recent decades has demonstrated cortico-cortical connections between lower-level sensory zones, between lower-level sensory zones and higher-order multisensory zones, and cortico-collicular connections between lower-level sensory zones and subcortical multisensory zones and between higher-order multisensory zones and subcortical multisensory zones, indicating neuroanatomical underpinnings of crossmodal effects in both unisensory perception and multisensory perception (Meredith, 2002). The possible neural pathways or networks comprising these brain areas in humans are schematically shown in Figure 2. The notion of these neural pathways or networks derives partly from human studies and partly from model animal studies because there are broad similarities between species (Patel, Yang et al., 2015). Specifically, studies in humans have revealed existence of direct white matter connections between primary auditory and primary visual cortex as well as other higher-order visual and auditory cortices (e.g., Beer, Plank, & Greenlee, 2011; Beer, Plank, Meyer, & Greenlee, 2013). Consistently, studies in model animals have demonstrated monosynaptic afferents from primary or low-level auditory association cortices to primary and secondary visual cortices (in monkey or marmoset: Cappe & Barone, 2005; Falchier, Clavagnier, Barone, & Kennedy, 2002, Falchier, Schroeder et al., 2010; Rockland & Ojima, 2003; cat: Clarke & Innocenti, 1990; Clemo, Sharma, Allman, & Meredith, 2008; and rodent: Henschke, Noesselt, Scheich, & Budinger, 2014; Vaudano, Legg, & Glickstein, 1991). For example, anatomical studies in nonhuman primates (macaques or marmosets) have shown direct projections from the core (primary) auditory, and from the lower-order association areas, such as caudal auditory belt and parabelt area, to the periphery of the primary visual cortex (Falchier, Clavagnier et al., 2002; Kayser & Logothetis, 2007). Studies in humans have further demonstrated that there are extensive ipsilateral connections between primary auditory cortex and primary and secondary somatosensory cortices, which provide an anatomical basis for interactions between audition and somatosensation (Ro, Ellmore, & Beauchamp, 2013). In line with this work, anatomical studies in gerbils have shown that there are cortico-cortical projections from primary auditory cortex to primary somatosensory cortex (e.g., Budinger, Heil, Hess, & Scheich, 2006), and from both primary auditory and primary somatosensory cortex to primary visual cortex (Henschke, Noesselt et al., 2014). The former anatomical study has further demonstrated laminar pattern of cortico-cortical connections, suggesting that primary auditory cortex receives primarily cortical feedback-type inputs and projects in a feedforward manner to its target areas of the brain (Budinger, Heil et al., 2006).

The reciprocity of these cortico-cortical connections, that is, projections from the visual to the auditory and somatosensory cortex, from the somatosensory to the auditory cortex, was revealed by other anatomical studies in model animals (Cappe & Barone, 2005; Cappe et al., 2009; Henschke, Noesselt et al., 2014; Sieben, Röder, & Hanganu-Opatz, 2013). For example, studies in ferrets and gerbils have demonstrated that primary auditory cortex receives projections from both primary and higher visual areas (Bizley, Nodal et al., 2007; Budinger, Heil et al., 2006; Cappe et al., 2009), and primary somatosensory cortex receives projections from primary visual cortex (Cappe et al., 2009; Henschke, Noesselt et al., 2014). Some studies in nonhuman primates have demonstrated that auditory areas, including the caudal medial and lateral belt areas, the caudal parabelt area, and the temporoparietal area, receive projections directly from secondary visual area and prostriata, a subdivision of the visual cortex (e.g., Falchier, Schroeder et al., 2010), whereas other studies have shown that belt or caudiomedial belt areas of the auditory cortex receive ipsilateral cortico-cortical projections directly from somatosensory cortex (Cappe & Barone 2005; Cappe et al., 2009; de la Mothe, Blumell, Kajikawa, & Hackett, 2006; Smiley et al. 2007). Electrophysiological studies in macaque monkeys further suggest that audio-visual and audio-tactile convergences occur in caudomedial auditory areas through feedforward and feedback anatomical projections (Schroeder & Foxe, 2002; Schroeder et al., 2001). Thus, it appears that sensory cortices are organized in a fashion that allows them to send and receive anatomical projections to and from each other (Figure 2).

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An early sensory cortex has anatomical connections not only with early sensory areas (primary and secondary) but with higher-order cortical areas and subcortical structures of the brain as well. In support of these multiple connections, some nonhuman primate studies have demonstrated that primary visual cortex and perhaps the peripheral area of the visual cortex receive (feedback) projections from both primary auditory area and polysensory higher-order areas of the temporal lobe, such as the perirhinal cortex (PRC) and the STS (Clavagnier, Falchier, & Kennedy, 2004; Falchier, Clavagnier et al., 2002). According to a prior review, the PRC has prominent reciprocal connections not only with the visual cortex but with a wide range of early sensory and polysensory association areas (Figure 2b, h; Suzuki & Naya, 2014) which allow this zone to receive highly processed information from almost all sensory regions (Holdstock et al., 2009). Other studies have revealed that the STS has reciprocal connections with unimodal parasensory association cortices subserving somatosensory, auditory and visual modalities (Figure 2a, g; Barnes & Pandya, 1992; Kaas & Hackett, 2000; Romanski, Bates, & Goldman-Rakic, 1999), as well as with other higher-order association areas, such as the (ventrolateral) PFC (Cusick, Seltzer, Cola, & Griggs, 1995; Diehl & Romanski, 2014), which also comprises multisensory neurons (Diehl & Romanski, 2014) and receives feedforward projections from visual cortex (Romanski, 2012), somatosensory cortex (Romanski, 2012) and auditory cortex, including the core, belt and parabelt auditory areas (Figure 2a, b; Hackett, Stepniewska, & Kaas, 1999; Kaas & Hackett, 2000; Plakke & Romanski, 2014; Romanski, 2012; Romanski, Bates et al., 1999; Romanski, Tian et al., 1999). A study in rats has shown that caudal temporal cortex, an area within the temporal lobe that extends from superior temporal gyrus (STG) down into STS and middle temporal gyrus, has reciprocal connections with multiple cortical areas, such as (primary and secondary) visual and auditory cortices, and the PRC, as well as with subcortical structures, such as different parts of the medial geniculate nucleus and the thalamus (Vaudano et al., 1991). The caudal temporal cortex projects to nuclei of the amygdala, and to nuclei of the IC and the deep layers of the SC (Vaudano et al., 1991) that are reciprocally connected in the midbrain (Stitt et al., 2015). The SC in all mammals comprises three superficial layers and four deep layers (Basso & May, 2017; Doubell, Skaliora, Baron, & King, 2003). The SC deep layers and other subcortical structures (e.g., the caudate nucleus, and substantia nigra in the basal ganglia; Nagy, Eordegh, Paroczy, Markus, & Benedek, 2006) are strongly connected to the thalamus and several other brain areas (May, 2006). These layers receive stimuli from somatosensory, auditory, and visual cortices (e.g., Alvarado, Stanford, Rowland et al., 2009; Baldwin, Young, Matrov, & Kaas, 2018; Meredith & Stein, 1983, 1986; Rowland, Quessy, Stanford, & Stein, 2007; Stein, 1978; Stein & Arigbede, 1972; Wallace, 2004; Wallace, Meredith et al., 1993; Wallace & Stein, 1996, 2001; Wallace, Wilkinson & Stein, 1996). However, it is still unknown whether they send any feedback projections to these sensory cortices (Figure 2b, j). Research has shown that the SC receives anatomical projections from the PFC and the PPC (Borra, Gerbella, Rozzi, Tonelli, & Luppino, 2014; Johnston & Everling, 2006), the latter one having cortico-cortical or anatomical connections with the visual cortex, auditory cortex, and the PFC (Hovde et al., 2018; Olsen et al., 2019; Whitlock, 2017). On the other hand, the IC that lies caudal to the SC has projections not only from the auditory cortex but from non-auditory areas as well, such as somatosensory cortex, visual cortex, and motor cortex (Lesicko et al., 2016; Olthof, Rees, & Gartside, 2019;

Yang et al., 2020). Taken together, it appears that the SC and the IC operate their functions under the control of both shared and distinct cortical areas, the IC receiving top-down input mostly from sensory cortices and the SC from both sensory and higher-order cortices (Figure 2b, j; see Chan, Koval, Womelsdorf, Lomber, & Everling, 2015; Everling & Johnston, 2013; Goldman & Nauta, 1976; Whitlock, 2017).

In summary, from the above discussion it appears that the lower-level sensory areas, sensory association areas, higher-order multisensory areas and multisensory subcortical structures are anatomically interconnected in some fashion (van Essen, Anderson, & Felleman, 1992). This anatomical connectivity allows them to process and integrate multisensory inputs through 'bottom-up' or feedforward pathways where different sensory modalities converge in higher-order multisensory areas, and/or through 'top-down' or feedback pathways where the lower-level sensory areas receive feedback projections from higher-order multisensory areas (Driver & Noesselt, 2008; Hackett, de la Mothe et al., 2014; Rockland & Ojima, 2003). When subcortical structures are recruited in 'top-down' processing they are likely to receive input projections from sensory areas and feedback projections from higher-order multisensory areas.

Development of crossmodal connectivity in the normal, healthy brain

Principles of crossmodal connectivity development. The sensory neocortex is a highly connected associative network that integrates information from multiple senses (Cappe et al., 2009; Meijer, Montijn, Pennartz, & Lansink, 2017). Crossmodal interactions occur not only during the early stages of sensory processing but during the later stages of processing as well (Henschke, Ohl, & Budinger, 2018; Sugiyama et al., 2018). Thus it is well established that crossmodal functional reorganization occurs due to preexisting crossmodal connectivity between sensory cortices. However, the current literature cannot tell clearly how crossmodal functional connectivity develops in the normal, healthy brain, particularly what principles guide this connectivity (Spence & Deroy, 2012). It is commonly believed that crossmodal connectivity builds on neuroplasticity of sensory cortices. What remain unclear are the principles that govern the connections between sensory cortices. Here, it can be proposed that perhaps three principles that follow guide the development of *crossmodal network or crossmodal connectivity* into adulthood.

The principle of innate crossmodality. First, it can be proposed that the origins of crossmodal connectivity are probably innate in humans and other mammals (Bieler, Sieben, Schildt, Röder, & Hanganu-Opatz, 2017; Meltzoff & Borton, 1979). The term *innate crossmodality* means that the network between sensory modalities has either been established prior to exposure to multisensory environment or those modalities are predisposed to make such a connection if given the opportunity to be connected later through multimodal experience (see below). In support of innate crossmodality, a recent study in pigmented rats *in vivo* demonstrated that visual-tactile processing in primary somatosensory cortex (S1) can emerge before crossmodal experience and be refined during juvenile development (Bieler et al., 2017). A number of other studies have shed light on the multisensory character of newborns and their developing brain (Wallace, 2004). Most of this work was done in cats and monkeys, demonstrating that multisensory neurons are present nearly at birth though they are strikingly immature (Stein, Stanford, & Rowland, 2014; Wallace, 2004; Wallace & Stein, 1996, 1997, 2001; Wallace, Ghose, Nidiffer, M. C. Fister, & J. K. Fister, 2012; Wallace, Carriere, Perrault Jr., Vaughan, & Stein, 2006). As postnatal life progresses, the incidence of multisensory neurons increases rapidly (Wallace & Stein, 2001), and their non-linear integrative capabilities start to appear (Wallace, Ghose et al., 2012; Wallace, Carriere et al., 2006). Thus the capacity of a neonate to use multiple sensory cues becomes increasingly robust and complex as maturation progresses (Wallace, 2004). Similar results have been reported in human infants that show age-dependent effects on reaction time when tested in localization of both unisensory (auditory or visual) and multisensory (audiovisual) stimuli (Carriere et al., 2007). Nevertheless, some basic multisensory processes seem to be in place quite early in human life as indicated by data from 4- to 8-month-old infants regarding the discrimination of auditory, visual and audiovisual rhythms or material stimuli (e.g., Rohlf, Habets, von Frieling, & Röder, 2017; Ujiie et al., 2018; Wallace & Stein, 2007).

The innate nature of crossmodality can also be inferred from a number of studies that used multi-subject experimental design in humans. For example, one study has shown that tactile shapes, like visual shapes, also activate the lateral occipital complex and like visual textures, tactile textures also activate the right medial occipital cortex (Stilla & Sathian, 2008). This indicates that the cells of these cortical areas are presumably innately crossmodal or predisposed to be crossmodal, that is, sensitive to sensory information irrespective of whether they are received through vision or touch. More recent studies have demonstrated that training in one sensory modality, such as tactile (Braille-reading) training, can induce plasticity in another sensory modality as in the visual cortex (Bola, Siuda-Krzywicka et al., 2017; Siuda-Krzywicka et al., 2016), and that crossmodal connections of sensory cortices can vanish with normal aging (Henschke, Ohl et al., 2018). It can be argued that without an innate, predisposition to crossmodality training in one sensory modality is not likely to induce plasticity in another modality, and that the innate crossmodal connections might vanish due to diminishing or weakening of neural connections with aging.

One may argue that the activation in nonstimulated visual cortex can be explained by saccades or eye movements (Sylvester, Haynes, & Rees, 2005). Such a possibility is very unlikely in cutting-edge neuroimaging studies, like those outlined above, in which participants are required to keep their eyes closed (Brodoehl, Witte, & Klingner, 2016), unless the purpose of the study is not to examine the effects of saccades or eye movements (e.g., Sylvester et al., 2005). However, as discussed before, the role of mental imagery in such crossmodal effects in normal humans cannot be precluded (e.g., Berger & Ehrsson, 2018; Nanay, 2018; O'Dowd et al., 2019; Schmidt & Blankenburg, 2019; Spence & Deroy, 2013; Wise et al., 2016). However, the pivotal role of mental imagery in the activation of nonstimulated sensory cortices does not contradict the innate nature of crossmodality. It can be proposed that the mental image of an environmental stimulus or object is perhaps elicited crossmodally only when the stimulated sensory cortex, such as A1, processes that input, and relays the input signal on to a second sensory cortex, such as V1, for further processing. However, this proposition might not be true for unimodal (intra-modal) mental imagery (Spence & Deroy, 2013) in which it is not necessary to relay input signals to a second sensory cortex; rather, the mental imagery can directly activate the nonstimulated sensory cortex, as in the case of envisaging a lost wrist watch.

The principle of evolution-driven 'neuromodular' reorganization. A second possibility is that crossmodal connectivity evolved during the course of primate evolution. It is widely agreed that primary sensory cortices are found in all extant species with brains (Kaas, 2008, 2012), and it has been speculated that in evolutionary history, primary sensory cortices arose first, followed later by the appearance of secondary or association cortices, and by extension, multisensory cortices (Mao, Hua, & Pallas, 2011; Pallas & Mao, 2012). A recent review of the experimental literature shows that the connections between different primary sensory cortices consistently occur in rodents, while primary-to-primary projections are absent or inconsistent in non-rodents, such as cats and monkeys (Meredith & Lomber, 2017). These observations suggest that crossmodal neuroplasticity that involves primary sensory areas is likely to exhibit species-specific distinctions (de Sousa & Proulx, 2014; de Sousa, Sherwood, Mohlberg et al., 2010; de Sousa, Sherwood, Schleicher et al., 2010).

In comparative neuroscience, evolution-driven functional reorganization has been studied using both cortical surface expansion model and inter-species activity correlation model as well (Ardesch et al, 2019; Mantini, Hasson et al., 2012; Orban, Van Essen, & Vanduffel, 2004). Research using a cortical surface expansion model interprets comparative fMRI data for monkey and human relying on spatial assumptions related to cortical expansion during evolution (Orban et al., 2004; Schira, Tyler & Rosa, 2012). It has been generally suggested that the parietal cortex has undergone intense evolutionary expansion (Bruner, 2018; Hinkley, Padberg, Krubitzer, & Disbrow, 2010; Kaas, 2008, Kaas & Stepniewska, 2016; Kolb & Whishaw, 2003; Singh-Curry & Husain, 2008). Consistently, a recent review has identified a number of human homologues of monkey IPS, and a few uniquely human areas in the inferior parietal lobule (IPL) resulting from evolutionary expansion (Orban, 2016). The expansion of the parietal cortex might have implication for integrating sensory information from other modalities. An area of significant expansion in the human brain appears to comprise of the polymodal parts of parietal area G

(PG), an area in the inferior parietal lobule in von Economo's maps (Eidelberg & Galaburda, 1984; von Economo, 1929), and the adjoining polymodal cortex in the STS. Past studies have also demonstrated multisensory maps in human parietal cortex (Sereno & Huang, 2014), particularly in human IPS (Makin, Holmes, & Zohary, 2007). The polymodal cells in the parietal cortex, particularly in the IPS and PG respond to both somatosensory and visual inputs, whereas those in the STS respond to various combinations of auditory, visual, and somatosensory inputs (Kolb & Whishaw, 2003; Makin, Holmes, & Zohary, 2007).

Of particular concern here is to clarify the controversy of the role of cortical expansion in driving adaptation or reorganization in the human connectome, a map of neural network in the brain (Ardesch et al., 2019; van den Heuvel, Bullmore, & Sporns, 2016). A recent review has suggested that cortical expansion plays an important role in the evolvement of temporoparietal junction and posterior STS in humans (Patel, Sestieri, & Corbetta, 2019). However, according to advocates of recent evolutionary theories, evolution-driven functional reorganization in the brain can be independent of cortical expansion (Anderson, 2010; Dehaene & Cohen, 2007). Research using an inter-species activity correlation model supports this idea. For example, using such a research model Mantini and colleagues examined similarities in sensory-driven functional magnetic resonance imaging responses between monkey and human brain areas by means of temporal correlation, and revealed regions for which functional processing has shifted to topologically divergent locations during evolution (Mantini, Hasson et al., 2012). A second study by Mantini and colleagues used a combined topological and functional approach to examine similarities and differences between monkey and human brains at the network level rather than at the area level (Mantini, Corbetta, Romani, Orban & Vanduffel, 2013). Using fMRI techniques they provided evidence for evolutionarily conserved cortical networks as well as identified two lateralized human frontoparietal networks that were evolutionarily new in the cortical regions. Consistently, a third and similar study at the cortical network level demonstrated evolution-driven differences in temporoparietal junction and frontoparietal networks between macaque monkeys and humans, albeit with broad similarities between these two species (Patel, Yang et al., 2015). Taken together, it can be concluded that the evolution-driven functional reorganization is not strictly related to cortical expansion process; rather, it may result from mechanisms whereby neuronal circuitries are adapted and recycled to enable more complex cognitive functions (Mantini, Hasson et al., 2012; Mantini, Corbetta et al., 2013). According to neural-reuse theories, neural circuits established for a certain function can be exploited, recycled, and redeployed during evolution, and be put to different functions, without losing their original use or function (Anderson, 2010; Anderson & Finlay, 2014). As pointed out by Anderson and Finlay (2014), brain evolution is an ultimate form of brain plasticity. The same principles that constrain cortical organization across species must also constrain brain organization more generally. The theories further suggest that for the acquisition of new uses or functions, neural circuits do not essentially need to involve pathological events, such as sensory deprivation and injury or a local change to circuit structure.

Further support for the above view comes from a very recent study of Ardesch and colleagues (2019) who investigated adaptations of human brain connectivity by means of comparative connectomics – the study of differences in the topological organization of connectomes (van den Heuvel et al., 2016). This study compared and contrasted humans and chimpanzees on shared connectivity in the primary, unimodal association, and multimodal association areas (Ardesch et al., 2019). The study demonstrated that the network centrality of shared connections linking bilateral primary areas was lower in humans than chimpanzees, whereas the shared connections linking bilateral multimodal association areas were more central in humans as compared to chimpanzees. The connections observed in humans but not in chimpanzees particularly link multimodal areas of the temporal, lateral parietal and inferior frontal cortices, including tracts important for language processing. However, the centrality of shared connections linking bilateral unimodal association areas was not statistically different between the two species. The same study further demonstrated a more pronounced modular topology of the human connectome as compared to the chimpanzee connectome. Based on these findings the researchers suggested an evolutionary shift in the human brain toward investment of neural resources in multimodal connectivity facilitating neural integration, combined with an increase in language-related connectivity supporting functional specialization (Ardesch et al., 2019).

A wealth of emerging studies in evolutionary neuroscience has suggested that *evolution-driven ‘neuromodular’ reorganization* is not restricted to cortical regions only, but can instead expand to subcortical structures as well (e.g., Baldwin & Bourne, 2017; Hrvoj-Mihic, Bienvenu, Stefanacci, Muotri, & Semendeferi, 2013; Raznahan et al., 2014; White, Kan, Levy, Itti, & Munoz, 2017). One such evolutionary subcortical structure is the SC (Gharaei et al., 2018) which is responsive to stimuli from multiple sensory modalities (Rowland, Quessy, Stanford, & Stein, 2007; Wallace, Meredith et al., 1993, 1998). Research in a range of species, including humans, has shown that the SC produces not only orienting responses but defensive reactions to looming (threatening) stimuli as well (e.g., Billington, Wilkie, Field, & Wann, 2011; Comoli et al., 2012; Dean, Redgrave, Sahibzada, & Tsuji, 1986, Dean, Redgrave, Westby, 1989; Liu, Wang, & Li, 2011; Sahibzada, Dean & Redgrave, 1986; Westby, Keay, Redgrave, Dean, & Bannister, 1990). The defensive-reactivity of the SC might have evolved during the course of primate evolution through modification and redeployment of neural circuits or networks (Anderson, 2010; Anderson & Finlay, 2014). Research investigating avoidance behavior in diverse species has suggested that multisensory network might have evolved in response to the survival demand in the environment, such as to help animals quickly detect and respond to diverse noxious stimuli (Srinivasan, Durak, & Sternberg, 2008). Although the study examined avoidance behavior to noxious stimuli that requires multisensory neurons, it can be proposed that for a nonhuman animal or human to make survival responses the stimuli should not necessarily be noxious, and therefore the same evolutionary process might reorganize its responses to any other general stimuli simultaneously coming from different senses. This idea receives support of the findings of a couple of prior studies in cats that used simple forms of auditory and visual stimuli (Alvarado, Stanford, Vaughan, & Stein, 2007; Jiang, Wallace, Jiang, Vaughan, Stein, 2001). For example, one study has demonstrated that converging cortical influences from the anterior ectosylvian (AES) and rostral lateral suprasylvian sulci have a critical role in mediating multisensory integration in the SC neurons (Alvarado, Stanford, Vaughan et al., 2007). Those sulci were found to play a crucial role in integrating SC responses to stimuli derived from different senses (visual–auditory), but no role in synthesizing its responses to stimuli derived from within the same sense (visual–visual). This result implies that very different neural circuits have evolved to code combinations of cross-modal and within-modal stimuli in the SC (Alvarado, Stanford, Vaughan et al., 2007). Taken together, it indicates the impact evolution might have on the functional reorganization of neurons during normal development of the human brain despite the emotional valence of stimuli. However, it does not rule out the impact of evolution on anatomical architecture. Indeed, evolutionary pressures might either lead to non-anatomical changes, only affecting the use of cortical structures (i.e. to depending on the different behavior repertoire of the animal), or to anatomical changes that might occur through cortical reorganization (and perhaps loss of the capacity for the original use), or development of new cortical areas due to profound (evolutionary) changes in behavior (Anderson, 2010; Dehaene & Cohen, 2007; Fitch, 2011).

The principle of multimodal experience. A third possibility is that humans begin life with independent sensory modalities (Meltzoff & Borton, 1979), with the crossmodal association acquired through experiencing the external world with multiple senses, such as vision and touch, simultaneously (see Figure 3), promoting their interactions and overlapping activation to a certain degree (Ferrari, Mastria, & Bruno, 2014; Ludden, Schifferstein, & Hekkert, 2009; Sieben, Bieler, Röder, & Hanganu-Opatz, 2015; Spence, 2015). Even if the crossmodal association is innate or evolved during primate evolution, it can further be shaped or reformed through learning or experience throughout the life span (Bieler et al., 2017; Ujiie et al., 2018). Humans live in a world which is multisensorial rather than unisensorial. They typically employ multiple sensory systems concurrently in order to combine different sensory inputs into a meaningful and coherent whole, and to maximize their enjoyment of the objects or events around them (Helbig & Ernst, 2008; Tsilionis & Vatakis, 2016). According to the *crossmodal facilitation* hypothesis, the ability to combine sensory inputs across sensory modalities dramatically enhances sensory performance (Gielen, Schmidt, & Van den Heuvel, 1983; Noesselt, Tyll et al., 2010; Stein & Meredith, 1993; Teder-Sälejärvi, McDonald, Di Russo, & Hillyard, 2002; Welch & Warren, 1986). Specifically, it has been suggested that multisensory information improves individuals' ability to detect (Frassinetti, Bolognini, & Ladavas, 2002; Gleiss & Kayser, 2014; Lippert, Logothetis, & Kayser, 2007; Lovelace, Stein, & Wallace, 2003), and discriminate (Leo, Romei, Freeman, Ladavas, & Driver, 2011) between stimuli compared with situations in which only unisensory stimuli are available. For example, individuals' ability to accurately detect the presence of a sound is improved when that sound is paired with a neutral light (Frassinetti et al., 2002; Lovelace et al., 2003). Along with increasing target detectability multisensory cues also improve individuals' ability to localize a target in space (Corneil, Van Wanrooij, Munoz, Van Opstal, 2002; Hairston et al. 2003).

Because information from different senses is typically complementary, the crossmodal integration of sensory inputs often provides information about the environment that is unachievable from a single sense in isolation (O'Hare, 1991). Thus it has been suggested that, in order to obtain a unified percept of the external world, diverse sensory inputs need to be bound together within distributed but strongly interconnected neuronal networks (Bizley, Maddox et al, 2016; Sieben, Bieler et al., 2015; Tsilionis & Vatakis, 2016). The extent to which multisensory inputs are bound together is determined by *spatial and temporal proximity* (Hebb, 1949; Kadunce et al., 2001; Meredith, Nemitz et al., 1987; Otto et al., 2013; Stein & Meredith, 1993; Stein, Stanford, & Rowland, 2014) and *semantic (informational) congruency* between sensory components, such as visual and auditory (Chen & Spence 2010; Doehrmann & Naumer 2008; Spence, 2011; Tsilionis & Vatakis, 2016). This multisensory binding takes place through experiencing the world with the simultaneous use of multiple sensory systems (e.g., Cuppini, Stein, & Rowland, 2018; Stein, Stanford, & Rowland, 2014; Tsilionis & Vatakis, 2016; Wallace, 2004). This notion of crossmodal connectivity is labeled as the *principle of 'multimodal experience'*. It is obvious that the exploration of the external world using multiple senses is innate in humans, just like other primates (i.e., typically they do not need learning to see with eyes, to feel through touch or to hear through the auditory system), but the crossmodal association formed through such a process is a form of neural network built on experiential learning, perhaps following Hebbian rule- what fires together, wires together (Bechtel & Abrahamsen, 1993; Cuppini, Magosso, Rowland, Stein, & Ursino, 2012; Hebb, 1949; see below for a more detail).

Thus the principle of '*multimodal experience'* underlying crossmodal connectivity is a learning principle that applies not only for basic information processing but for aesthetic processing as well. An example can be given of how this principle might have worked for aesthetic processing. Suppose somebody is visiting a clothing store to purchase a gift. Without touching the clothes at the store s/he can easily visually judge that it looks very beautiful, but if s/he wants to see whether it is comfortable or not s/he must touch it because vision may not be an optimal sense for doing this job as it provides little information about comfortableness (Karim & Likova, 2018; Montagu, 1971; Schneider, Lorenz, Senkowski, & Engel, 2011). Secondly, each of the two senses likely provides qualitatively different subjective impressions of the clothes. Thus clothing which is visually beautiful may not be necessarily tactilely pleasing (comfortable) or vice versa. These two aesthetic aspects of the clothing have different significance to the consumers or clothing wearer, and are determined separately by the two sensory modalities (Cuppini, Ursino, Magosso, Rowland, & Stein, 2010; Hertz & Amedi, 2010; Karim & Likova, 2018). Perhaps the third rule of multisensory integration, the *rule of inverse effectiveness*, works here because each sense alone provides only partial information about the overall quality of the clothes (Stein, Stanford, & Rowland, 2014). Thus, if the person wants to evaluate the overall quality of the clothes, s/he must use both the visual and tactile senses simultaneously (*temporal coincidence*; Otto et al., 2013; Spence, 2011; Stein & Meredith, 1993; Stein et al., 2014), allowing them to interact and develop an association (when *spatial proximity* is optimum or high). While doing this job, the basic information of the clothing (e.g., color, thickness, textureness, softness) are initially processed at the respective sensory levels separately (i.e., visual information at visual sensory level and tactile information at tactile sensory level) which dispatch the resulting outcomes through a bottom-up pathway onto the higher order cortical level which further processes the lower level visual and tactile outcomes through a top-down pathway, and integrates them (Cuppini, Stein et al., 2018) to decide about the overall quality of the clothing, and to discriminate the preferred clothe(s) among many. Thus the two sensory modalities work concurrently and independently, but also interact during higher order processing in order to make the external world more meaningful and more beautiful (Wallace, 2004), following the rules of multisensory integration cited above (see also Table 2). This is just a simple example of the simultaneous use of multiple senses. People are likely to make many more decisions of this type every day. Thus, it can be concluded that crossmodal interactions and crossmodal connectivity develop in humans to enable them to experience and enjoy the multisensory world in a meaningful way by accurately combining inputs from different sensory systems (Göschl, Engel & Friese, 2014), though this does not necessarily rule out their functional independence.

To summarize, despite their functional independence, sensory systems interact and cooperate with each other to optimize viewers' perception of the objects and events by providing a robust representation of the external world (Ferrari et al., 2014; Ludden et al., 2009; Spence, 2015). There is now a mounting body of evidence supporting the crossmodal interplay of the sensory modalities; however, this evidence mostly comes from multisensory research in basic perception (e.g., Dematte, Sanabria, Sugarman, & Spence, 2006; Heller, 1982; Hauthal et al.,, 2014; Jousmäki & Hari, 1998; Kandula, Hofman, & Dijkerman, 2015; Lugo, Doti, Wittich, & Faubert, 2008; Sambo & Forster, 2009; Spence, 2015), and very rarely from multisensory research in arts and aesthetic perception (e.g., Streicher & Zachary, 2016). Thus, the extent to which the sensory modalities interact to shape aesthetic sensitivity (or preferences for certain stimuli or objects over the others) remains poorly understood and presents an exciting area of future research.

A model of crossmodal connectivity development. Now, it appears that crossmodal connectivity in the normal, healthy brain might be innate or evolved or even learned. However, a careful analysis of the relevant studies cited above indicates that the influences of these factors are not necessarily mutually exclusive; they are rather inclusive and interactive. This suggests that crossmodal connectivity can be a product of interactions among these three factors. Thus, combining the aforementioned three principles a three-factor interaction model of crossmodal connectivity, perhaps the first model of its type, is proposed (Figure 3). In this unique model, visual and somatosensory cortices are used as sensory-specific areas, with a multisensory zone as a third intervening area. According to this model, the visual and somatosensory areas are neurally and physiologically connected to the multisensory zone. When individuals are exposed to congruent multisensory inputs in the external environment the component inputs are received by the respective unisensory neurons in close proximity, that is, visual input by visual neurons, tactile input by somatosensory neurons. Then, the unisensory neurons within each of the two sensory-specific areas concurrently process the information, feeding them forward to the multisensory intervening neurons that are responsible for binding, integration, and final decision, about the incoming crossmodal signals. The input signals from unisensory neurons, if given attention to perceptual attributes of both the signals, are perhaps processed by a default competitive circuit within the multisensory zone (Rapp & Hendel, 2003; Yu, Cuppini, Xu, Rowland, & Stein, 2019). Thus information from multiple senses are synthesized and integrated in a third intervening area, despite the initial processing in sensory areas by their unisensory neurons. This proposition about crossmodal connectivity is in line with the crossmodal functional architecture (Cuppini, Stein et al., 2018) and the receptive field overlap hypothesis (Wallace, 2004). According to the crossmodal functional architecture, information from different modalities is brought into close proximity via a patchy distribution of inputs, followed by integration in the intervening multisensory zone (Cuppini, Stein et al., 2018). The receptive field hypothesis states that there is an overlap between different sensory receptive fields (RFs), such as visual and somatosensory RFs, in a multisensory SC neuron (Wallace, 2004). This means that SC multisensory neurons typically have RFs for different modalities in spatial register. Thus, a visual–somatosensory neuron has two RFs, one for the auditory and one for the tactile modality, and that these RFs have a large superimposed region in the SC (Meredith & Stein, 1996). These RFs are topographically organized so that proximal neurons in the SC have RFs with proximal centers in the environment. Here, it can be noted that the SC is not the only area responsible for mediating crossmodal connectivity. Indeed, there are other multisensory zones, such as the rhinal cortex and the amygdala that are likely to comprise neurons of the same receptive field properties and play the mediating role for the development of crossmodal connectivity through multimodal experience of the external world (Shams & Seitz, 2008; Ujiie et al., 2018). However, it merits further investigation to see which of these brain areas or structures serve the mediating role in which environmental setting or context.

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The model proposed in this narrative review suggests two opposing or equally possible propositions. First, two sensory modalities, such as visual and tactile, if not innately connected, can be connected to each other through evolution-driven reorganization of the visual and somatosensory cortices, and the role of multimodal experience of the external world is to strengthen that connectivity (see above). Second, if the sensory modalities are innately connected in earliest mammals, the human ancestors (Pallas & Mao, 2012), that connectivity can further be changed or modified through evolution-driven reorganization of these sensory cortices (Ardesch et al., 2019; see also above) and multimodal experience of the world as well (Bieler et al., 2017; Ujiie et al., 2018). Even the intervening role of a multisensory zone might have been developed through evolution-driven reorganization. For example, it has been shown that cortico-collicular circuit derived from AES cortex, a higher-order associative area, has evolved for the purpose of combining information across multiple senses, such as visual and tactile (Stanford, Alvarado, Vaughan, Rowland, & Stein, 2009). Evolution and multimodal experience can also interact to shape or strengthen the innate connectivity between sensory modalities. As discussed above, evolution might reorganize the anatomical and functional architecture of the brain, establishing a connection between sensory modalities. Once a connection is established between two sensory modalities - such as vision and touch - through evolution, it can further be strengthened by multisensory learning or experience of the world (Proulx, Brown, Pasqualotto, & Meijer, 2014). For example, when someone touches spatio-temporally and semantically congruent (real) textured objects, such as a stone, s/he simultaneously visualizes their textures and shapes, which engage the relevant area(s) of the visual cortex (Figure 3). Repeated activation of this type fosters an increased-weight association between the two sensory modalities, not only during basic object understanding, but during aesthetic appreciation of the object as well (see above). The same argument applies for a crossmodal network between other sensory modalities, two or more, of any combination. An environmental object or event can produce multimodal signals, stimulating more than two senses simultaneously. For example, when a visible object moves with some sound to touch the body, the individual's attention needs to be coordinated across three sensory modalities, in order to select visual, auditory, and tactual information originating from the same object or event (Magosso, Serino, di Pellegrino, & Ursino, 2010) where the same principles and propositions might apply, but in a more complex fashion, which is beyond the discussion of this review so as to keep the model parsimonious and comprehensive.

The evidence for experience-dependent crossmodality comes from a plethora of studies that investigated the development of multisensory association and the (multisensory) neurons recruited for building this association (Bieler et al., 2017; Brandwein et al., 2011; Ujiie et al., 2018). For example, a high-density electrical mapping study by Brandwein et al. (2011) examined the maturation of audio-visual integration by comparing behavioral and neurophysiological responses in participants aged from middle childhood to early adulthood. This study showed a gradual fine-tuning of multisensory facilitation on a simple audiovisual reaction time task that reached adult levels by the age of 14, indicating the role experience plays as a modulatory factor albeit it cannot preclude the innate predisposition of crossmodality (Bieler et al., 2017). Although behavioral studies have shown that neonates can detect certain crossmodal correspondences very early in life (Lewkowicz & Lickliter, 1994), physiological studies have shown that multisensory neurons are strikingly immature at birth (Stein, Stanford, & Rowland, 2014; Wallace & Stein, 2001). Thus neurons in a newborn's brain are not capable of multisensory integration (Cuppini, Stein et al., 2018; Wallace, Perrault, Hairston, Stein, 2004; Yu, Rowland, & Stein, 2010; Xu, Yu, Rowland, Stanford, & Stein, 2014). Indeed, many findings in the literature indicate that the capacity to integrate sensory information is not innate in the nervous system; rather, it gradually develops and may plastically change with sensory experience - the experience with the external world, rich of crossmodal stimuli, shapes network in a functionally relevant manner (Cuppini, Magosso et al., 2011). Thus far, perhaps the most intensively studied multisensory neurons are SC neurons, which are known to play important roles in integrating inputs from multiple sensory modalities, such as visual, auditory, and somatosensory (Perrault, Stein, & Rowland, 2011; Perrault, Vaughan, Stein, & Wallace, 2005; Rowland, Stanford, & Stein, 2007; Stein & Stanford, 2008; Stein & Meredith, 1993). The capacity of SC neurons for multisensory integration are not present at birth; the brain develops this capacity postnatally after the animal acquires sufficient experience with covariant crossmodal stimuli or events to form links between their modality-specific components (Cuppini, Magosso et al., 2011; Cuppini, Stein et al., 2018; Stein, Perrault et al., 2009; Wallace, Perrault et al., 2004; Xu et al., 2014; Yu et al., 2010). The crossmodal experience alters the underlying neural circuit in a way that optimizes multisensory integrative capabilities for the environmental setting in which the animal functions (Stein, Stanford, & Rowland, 2014). However, for the development of multisensory capacity the SC needs normal sensory experience and appropriate crossmodal stimuli, defined in terms of spatio-temporal congruence and semantic (informational) congruence between sensory components (Figure 3). The elimination of experience in one sensory modality (e.g., vision) during postnatal development severely compromises the integration of multisensory cues (Wallace, 2004).

Similarly, in the absence of appropriate crossmodal stimuli, SC neurons remain multisensory but lose their integrative capacity (Cuppini, Magosso et al., 2011).

Thus, crossmodal connectivity in the normal, healthy brain is a preexisting multisensory organizational and functional entity originated innately or through evolution; however, multisensory experience appears to play a major role in shaping or strengthening that connectivity. In further support of this, research has shown that the development of multimodal responses and connections is not limited to everyday pragmatic multisensory experience; they can even be induced in a variety of brain areas with appropriate multisensory training (Paraskevopoulos & Herholz, 2013; Saito, Okada, Honda, Yonekura, & Sadato, 2006; Shams & Seitz, 2008).

Conclusion

The rapid growth of research in the past few decades on the topic of neuroplasticity and crossmodality has produced many fascinating insights into how the brain integrates information received through different senses (Macaluso & Driver, 2005). But it is just the beginning of understanding the complexity of interactions in the sensory systems, and the crossmodal connectivity in perceptual and cognitive processing. Perhaps this is the first comprehensive narrative review that summarizes and synthesizes most of the prior and prominent studies about neuroplasticity and crossmodal connectivity in the normal, healthy brain. Backed by the relevant past studies, here two different forms of crossmodal connectivity (*direct* and *indirect*) are suggested to operate in both unisensory perception and multisensory perception. Three principles likely underlie these sorts of crossmodal connectivity development: *the principle of innate crossmodality, the principle of evolution-driven 'neuromodular' reorganization, and the principle of multimodal experience*. Also, built on these principles a three-factor interaction model is proposed, explaining how the principles interact for the development of crossmodal connectivity in the normal, healthy brain. Although the model proposed in this review is limited to explaining interactions and association between two sensory modalities of any combination like audio-visual, visuo-tactile, and audio-tactile, it can further be extended to the association of more than two sensory modalities where the same principles and propositions might apply, but in a more complex fashion. This remains to be tested in future research toward the advancement of this exciting field of neuroscience.

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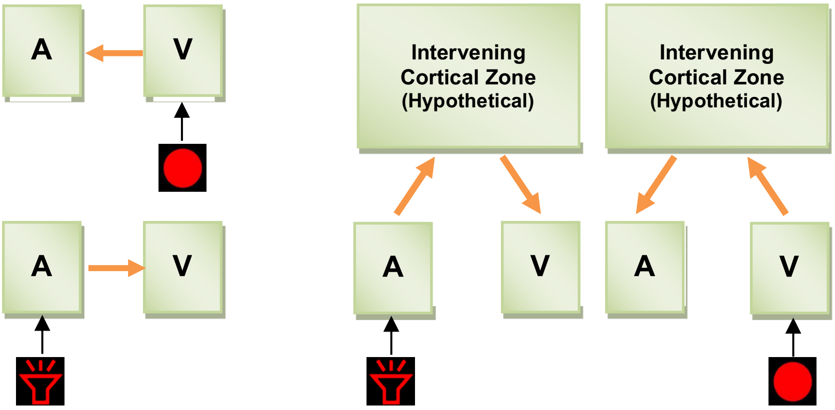
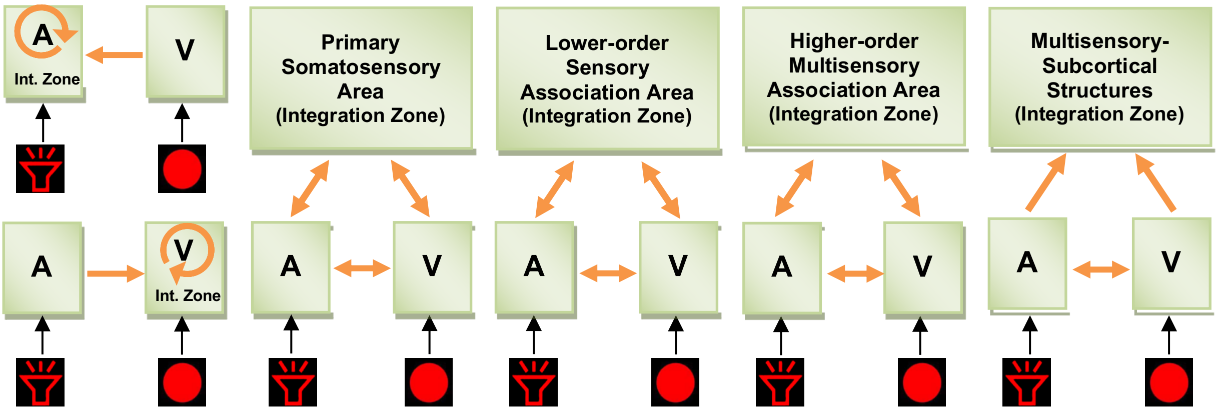
(I) Crossmodal connectivity in unisensory perception



(a) (b)

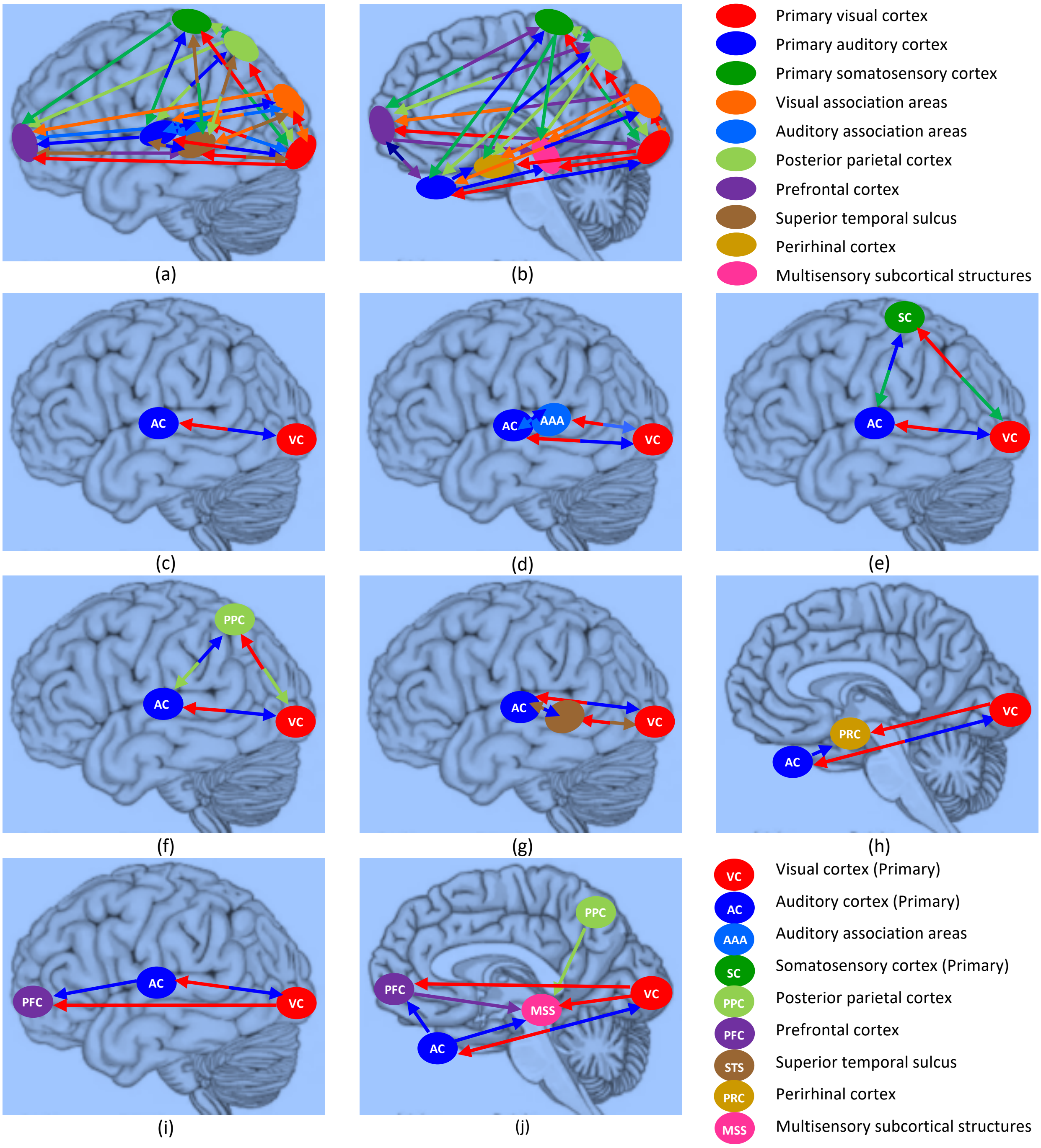
(II) Crossmodal connectivity in multisensory perception



(c) (d) (e) (f) (g)

Figure 1. Two types of hypothetical connectivity schematics between auditory (A) and visual (V) modalities, in both unisensory and multisensory perception. (a) Two cases of direct connectivity between A and V modalities in unisensory perception, which show that stimulation in cortical territory associated with modality A is dispatched to and activates the nonstimulated cortical territory associated with modality V (lower panel) and vice versa (upper panel). (b) Indirect connectivity between A and V modalities in unisensory perception, which show that stimulation in cortical territory associated with modality A is dispatched to and activates the nonstimulated cortical territory associated with modality V (left panel) and vice versa (right panel) via a third intervening zone. (c) Two cases of direct connectivity between A and V in multisensory perception where both auditory and visual stimuli likely interact in visual cortex, an area of modality V (lower panel) or in auditory cortex, an area of modality A (upper panel). Here, the unidirectional arrows indicate that a signal is being projected from modality A to modality V (lower panel)

or vice versa (upper panel). The circular arrow used inside V indicates that stimulation in this modality does not send any signal projection to A; rather, it is ready for interaction with the input signal to be received from A in its own zone V (lower panel). Similarly, the circular arrow used inside A indicates that stimulation in this modality does not send any signal projection to V; rather, it is ready for interaction with the input signal to be received from V in its own zone A (upper panel). (d) Indirect connectivity of feedforward convergence of inputs from A and V in a third primary sensory zone, such as primary somatosensory cortex (an integration zone), with feedback projections from that primary sensory zone to A and V. (e) Indirect connectivity of feedforward convergence of inputs from A and V in a lower-order sensory association zone (a second integration zone), with feedback projections from sensory association zone to A and V. (f) Indirect connectivity of feedforward convergence of inputs from A and V in a higher-order multisensory association zone (a third integration zone), with feedback projections from higher-order multisensory association zone to A and V. (g) Indirect connectivity of feedforward convergence of inputs from A and V in a multisensory subcortical zone (a fourth integration zone), with no feedback projections from multisensory subcortical zone to A and V (there is no evidence that a subcortical zone sends feedback projections to the connected sensory cortices). The bi-directional arrows used between A and V in panels d – g indicate that A and V are neurally interconnected and are likely to communicate and share information, but not to converge and integrate multisensory stimuli by themselves.



(a) (b) (c) (d) (e) (f) (g) (h) (i) (j)

Figure 2. Possible Neural Pathways mediating crossmodal connectivity through feedforward and feedback projections. a and c – i represent cortico-cortical connectivity; b represents both cortico-cortical and subcortical connectivity; and j represents cortico-collicular (subcortical) connectivity. The unidirectional arrows indicate evidenced-based one-way communications, either feedforward or feedback, whereas bi-directional arrows indicate two-way communications, between the areas involved in forming a crossmodal connectivity. Because it is a schematic view, each color-coded area shows its approximate location, but does

not represent its actual size. The MSS designation in this schematic view, however, includes only the prominently studied small midbrain regions of the superior and inferior colliculi.

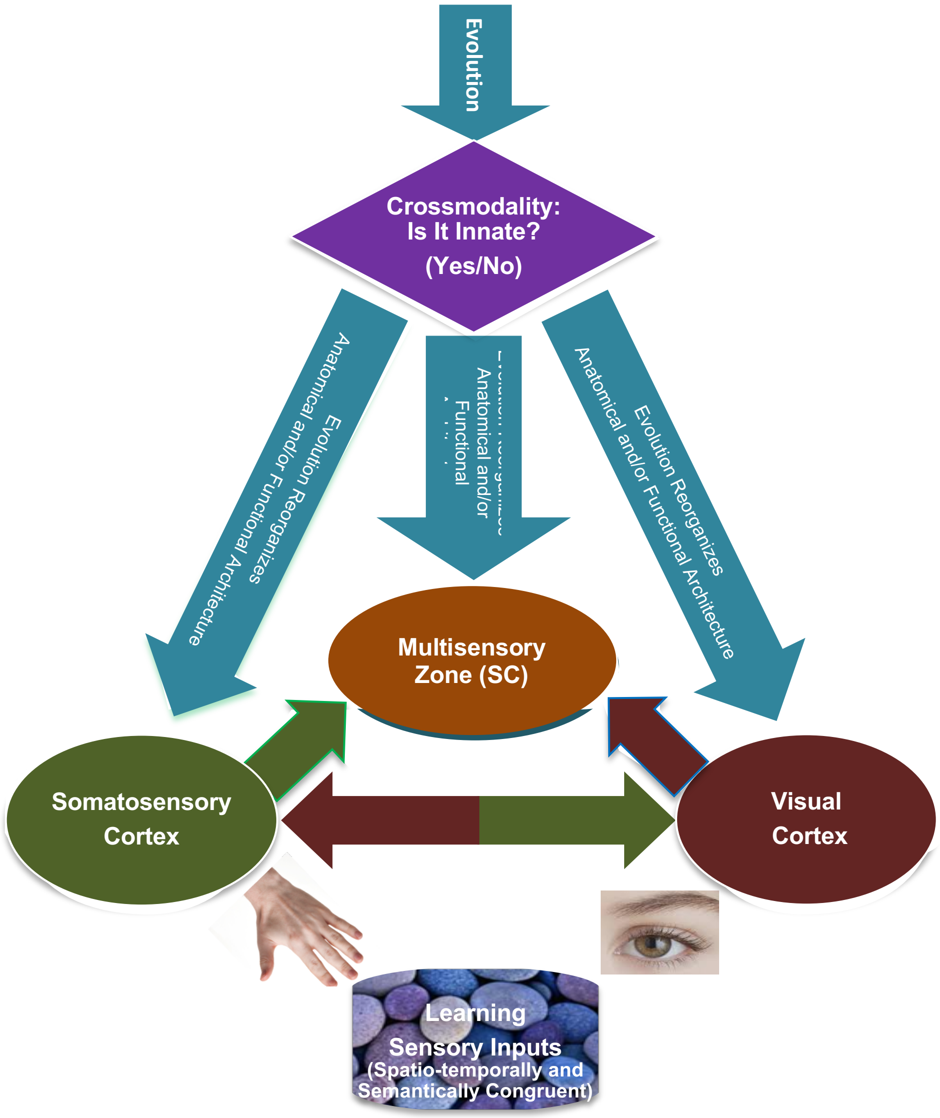


Figure 3. A hypothetical model of crossmodal connectivity development. The model shows both a direct connectivity, and indirect connectivity (via SC, a multisensory midbrain zone) between visual and tactile modalities/cortices for spatio-temporally and semantically congruent (real) textures. The multisensory zone SC shows only one-way connectivity to the somatosensory and visual cortices, indicating that it receives feedforward inputs from these sensory cortices without sending any feedback projections to them (for two-way connectivity of a multisensory intervening zone to the sensory cortices see Figure 1f). In the above figure, the same crossmodal connectivity represents learned and/or evolved connectivity (when the answer is ‘No’ to the question - Is it innate?) as well as innate connectivity (when the answer is ‘Yes’ to the question - Is it innate?) that can be shaped or reformed through evolution, and multisensory learning or experience of the world around us.

Table 1

The principles of neuroplasticity

	Principle	Description	Reference
1	Use it and improve it, or lose it	Engaging neural circuits can lead to functional enhancement, and a failure to engage it can lead to functional degradation	Kleim & Jones, 2007
2	Sufficiency of training or repetition	Plastic changes require sufficient training or repetition	Kleim & Jones, 2007
3	Salience of experience	Plastic changes require sufficiently salient experience	Kleim & Jones, 2007
4	Time-dependence	Plastic changes are time-dependent	Kleim & Jones, 2007; Kolb & Gibb, 2008
5	Age-dependence	Plastic changes are age-dependent	Kleim & Jones, 2007; Kolb & Gibb, 2008
6	Transference	Plasticity within a set of neural circuits has the ability to promote concurrent or subsequent plasticity	Kleim & Jones, 2007
7	Interference	Plasticity in response to experience can interfere with new learning or the acquisition of other behaviors	Kleim & Jones, 2007
8	Task-specificity	Plastic changes are task-specific	Amedi, Hofstetter et al., 2017; Bola, Zimmermann et al., 2017; Collignon, Vandewalle et al., 2011; Heimler et al., 2015; Kleim & Jones, 2007; MacSweeney et al., 2002; Merabet, Thut et al., 2004; Pascual-Leone & Hamilton, 2001; Ricciardi et al., 2014

Table 2

The principles of crossmodal integration in multisensory perception

	Principle	Description	Reference
1	Temporal coincidence	Sensitivity of neurons to multisensory inputs is dependent on their relative timing	Otto et al., 2013; Stein & Wallace, 1996; Stein, Stanford, & Rowland, 2014
2	Spatial proximity	Sensory inputs in spatial proximity produce multisensory enhancement and are likely to be integrated. Two sensory inputs are said to be in spatial proximity if both fall within the RF of the same multisensory neuron or within the overlap of the RFs of different sensory modalities.	Cuppini, Magosso et al., 2011; Kadunce et al., 2001; Meredith, Nemitz et al., 1987; Otto et al., 2013; Stein, 1998; Stein & Meredith, 1993; Stein, Stanford, & Rowland, 2014
3	Inverse effectiveness	The magnitude of multisensory integration is greatest when unisensory signals are rather weak.	Otto et al., 2013; Stein, Stanford, Ramachandran et al., 2009