Review article

Are critical periods reversible in the adult brain? Insights on cortical specializations based on sensory deprivation studies

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ABSTRACT

We review here studies with visual and auditory deprived/recovery populations to argue for the need of a redefinition of the crucial role of unisensory-specific experiences during critical periods (CPs) on the emergence of sensory specializations. Specifically, we highlight that these studies, with emphasis on results with congenitally blind adults using visual sensory-substitution devices, consistently document that typical specializations (e.g., in visual cortex) could arise also in adulthood via other sensory modalities (e.g., audition), even after relatively short (tailored) trainings. Altogether, these studies suggest that 1) brain specializations are driven by sensory-independent computations rather than by unisensory-specific inputs and that 2) specific computation-oriented trainings, even if executed during adulthood, can guide the sensory brain to display/recover, core properties of brain specializations. We thus introduce here the concept of a reversible plasticity gradient, namely that brain plasticity spontaneously decreases with age in line with CPs theory, but it nonetheless can be reignited across the lifespan, even without any exposure to unisensory (e.g., visual) experiences during childhood, thus diverging dramatically from CPs assumptions.

1. Classic assumptions on the emergence of sensory brain organization

For decades, the prevailing assumption on the emergence of our sensory-brain organization has been that functional brain specializations arise from evolutionary programing that developed through natural selection. This conclusion was supported by the repeatedly observed anatomical consistency of brain specializations across individuals, not only for the large-scale division of sensory labor (e.g., visual, auditory or somatosensory regions) but even within specific sensory cortices (e.g., in vision: retinotopic mapping or the large-scale specialization in two visual streams, which comprises category selectivity to stimuli that are particularly important to primates like faces, tools, movement detection or body images among others).

Furthermore, in addition to these evolutionary-driven predispositions, the main assumption was that for our sensory brain organization to properly emerge, humans must receive full exposure to unisensory-specific stimulations early in life (e.g., vision for visual system specializations), during specific time-frames defined as critical/sensitive periods of development, when the brain is particularly plastic (Hensch, 2004; Knudsen, 2004). These conclusions stemmed from the seminal

studies by Hubel and Wiesel (Hubel and Wiesel, 1962; Wiesel and Hubel, 1965, 1963) demonstrating that if during critical/sensitive periods an individual lacked, exposure to a given unisensory-modality (e.g., vision), the corresponding sensory system would not develop neither in terms of typical behavioral functions nor typical brain specializations (see also (Cynader and Chernenko, 1976; Cynader and Mitchell, 1977; Hubel and Wiesel, 1970; Knudsen, 2004, 1988)). We refer here to this proposal as the classic critical periods (CPs) theory (see Table 1 for a summary on the main assumptions and predictions of the CPs theory). Studies in blind patients who recovered vision during adulthood further support these seminal findings by documenting lack of proper development of visual-related brain specializations, even years after visual restoration (Bottari et al., 2018, 2016; Fine et al., 2003; Grady et al., 2014; Levin et al., 2010; Lewis and Maurer, 2005; Roder et al., 2013).

In other words, the classic CPs theory posits that the closure of critical/sensitive periods corresponds to a major drop in the plastic capabilities of our sensory brain, ultimately leading to the conclusion that it is impossible to (re)-establish typical behavioral functions and related brain specializations in adulthood (Table 1). This is the conclusion we want to challenge here.

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Table 1

Direct comparison between assumptions, evidence and predictions related to the classic theory of critical periods (CPs) and those related to the proposal of the reversible plasticity gradient (RPG).

Critical Periods (CPs) theory stemming from Hubel and Wiesel seminal works	vs.	Reversible Plasticity Gradient (RPG) theory stemming from new sensory deprivations studies

Common points of you:
- The brain is more plastic during infancy when learning is quicker and very efficient even when unsupervised
- Certain sensory modalities are better suited than others to carry out specific tasks/computations –thus in cases of typical development we all end up with similar sensory brain specializations

Diverging points of view:

1A) Anchored to unisensory inputs: Sensory-specific experiences are the main drive for the emergence of typical brain specializations		**1B) Anchored to specific task-oriented computations:** Brain specializations are driven by hard-wired predispositions to process specific sensory-independent computations
2A) Sensory-specific: If a unisensory input (e.g., vision) is not experienced during CPs, typical brain specializations will not properly develop (e.g., retinotopic organization or object-categories divisions in the visual cortex).		**2B) Sensory-independent:** Absence of sensory-specific experiences early in life does not inevitably prevent the emergence of sensory brain specializations as long as computation-specific information can be accessed via another sensory modality
3A) Unmodifiable across life: After the closure of CPs, typical brain specializations across sensory cortices cannot be (re)-established*		**3B) Modifiable across life:** Task/computation-oriented trainings successfully guide/facilitate the (re)-establishment of typical brain specializations at any time across the lifespan*
4A) Brief periods of deprivation: if unisensory inputs are absent even briefly and/or partially during CPs, typical brain specializations across sensory cortices will be never (re)-established*		**4B) Brief periods of deprivation:** via unisensory or multisensory task/computation-oriented trainings, typical brain specializations can be successfully (re)-established*
*The updated view on CPs acknowledges the presence of remaining plasticity in the adult brain that can be triggered via unisensory trainings. Though, it still posits that in order for late interventions to lead to effective recovery, patients must have been at least partially exposed to sensory-specific experiences during CPs.		* Available evidence supports these statements for higher-order sensory regions and initial evidence hints to the same direction also in early sensory regions. Future studies will need to determine whether in early sensory regions computation-oriented trainings will need to be paired with more invasive approaches, such as tailored chemical interventions aiming at increasing plasticity to (re)-establish typical brain specializations.

Evidence and Predictions:

1A) In case of congenital blindness or deafness, no brain specialization is expected to develop across the deprived sensory cortices and if it does, its anatomical location will not be consistent across individuals.		**1B)** In case of congenital blindness or deafness, typical brain specializations, at least in higher-order sensory regions, can still naturally emerge via atypical sensory-inputs (e.g., activating "visual" cortices via audition)
2A) Deprived sensory cortices are cross-modally recruited by intact sensory modalities, but in a random fashion, with no specific organizational principle and no anatomical consistencies across individuals		**2B)** Deprived sensory-cortices are cross-modally recruited by intact sensory modalities, maintaining their typical functional specializations anatomically consistently across individuals –Task-selective Sensory-Independent (TSSI) organization; Fig. 1).
3A) No typical and anatomically consistent specializations can emerge in late deprived sensory cortices, namely if deprivation occurs after the closure of CPs		**3B)** TSSI anatomically consistent specializations can emerge even in adulthood after tailored computation-oriented training –also when pairing a specific computation with a novel sensory input that never performed such computation before
4A) Sight recovered patients who did not experience vision during CP even shortly, will not recover typical visual brain responses and specializations –albeit they might recover certain visual tasks behaviorally		**4B)** Computations and related brain specializations which were not learned/established early in life, can still be learned/established in adulthood if a tailored training is provided
5A) Auditory recovered patients who did not experience audition during CP, will not recover typical auditory brain responses		**5B)** Sensory recovered individuals who did not experience unisensory inputs early in life, can still develop typical brain specializations for the reafferented sense even in adulthood, if multisensory computation-specific training is provided
6A) Partial sensory deprivations, such as congenital amblyopia in one eye or hemianopia, will not recover if interventions take place after the closure of CP		**6B)** Partial sensory deprivations, such as congenital amblyopia in one eye or hemianopia, can partially recover via unisensory trainings in adulthood. Recovery outcomes can further improve and perhaps even fully revert if multisensory training is provided sometimes paired with activities/chemical interventions facilitating/boosting cortical responsiveness

Importantly, some aspects of this stringent assumption have been already (partially) put into question during the last decades. Specifically, accumulating evidence highlighted that the human adult brain still retains a considerable amount of plasticity (Buonomano and Merzenich, 1998; Draganski and May, 2008; Recanzone et al., 1992, 1993; Reetzke et al., 2018; Thomas and Baker, 2013). Many studies of this kind showed the remarkable benefits of specific unisensory training regimens, undertaken during adulthood, for the efficient (re-) wiring of the brain in several domains: for the recovery, in the aging brain, of higher-order abilities such as language, memory and executive functions as well as hearing; for the improvement of specific sets of sensory/cognitive abilities either as a consequence of specific acquired expertise or as a consequence of partial or more widespread lesions (see for reviews (Bherer, 2015; Habib and Besson, 2009; Kerr et al., 2011; Levi, 2005; Lövdén et al., 2010; Witte, 1998). This body of studies unravels the lifelong capacity for plasticity of the human brain and the crucial role of specific unisensory training programs for efficiently triggering it even in adulthood (see also (Heimler and Amedi, 2020)).

However, all these studies still posited that each unisensory-specific function must be at least partially experienced during critical periods in order for the corresponding brain specialization to emerge -and later in

life to be further modified by training. In other words, the commonly accepted view on human brain organization still postulates that sensory brain regions are sensory-specific in nature, and that there is an unalterable link between a given brain sensory region and a unisensory-specific computation/cognitive task which must be established during critical periods via unisensory-specific experiences (e.g. visual/auditory inputs during CPs to develop visual/auditory behavioral functions and corresponding brain specializations; see Table 1).

In this review, we will provide an overview on the findings coming from studies with human sensory deprived populations (and to a lesser extend also coming from animal models), which have been accumulating over the last two decades, and that strongly challenge the validity of these classic assumptions -also in their revised form, namely acknowledging the presence of some remaining plasticity in the adult brain. Specifically, based on these studies, we will argue here against the conclusion that the lack of unisensory inputs, such as vision or audition, during CPs will irreversibly prevent the recovery/emergence of brain specializations in cortical areas, across the lifespan. Mainly, we will argue here against the conclusion that unisensory-specific inputs during CPs are actually the key drive to brain organization (see Table 1). We will not challenge here the assumption that each sensory

cortex is specialized to process certain computations which are optimally shaped by unisensory-specific inputs early in life (such as object recognition, motion detection or spatial localization in occipital cortices via vision). However, we will present accumulating and compelling findings in sensory deprived populations which suggest that similar computation-oriented specializations, anatomically consistent across individuals, can emerge also via other sensory modalities (e.g., audition or touch rather than vision), even during adulthood. We will discuss how these results suggest that brain specializations are driven by sensory-independent computations rather than by specific unisensory-inputs as classically conceived. We will also present results demonstrating that such specializations can be triggered by atypical sensory inputs provided to the brain by naturally acquired compensatory information (e.g., using touch for object recognition (Amedi et al., 2001; Zangaladze et al., 1999)). In addition, we will emphasize studies documenting the emergence of cortical specializations using non-visual information conveyed artificially by dedicated technologies paired with tailored training programs also during adulthood (i.e., sensory substitution technologies, namely devices that transform information typically conveyed by one sense (e.g., vision) via other sensory-modalities (e.g., audition or touch) while maintaining core features of the transformed sense, e.g., objects' shapes, locations or color information in case of visual sensory-substitution technologies (Abboud et al., 2014; Bach-Y-Rita et al., 1969; Meijer, 1992a,b); see section 2.1).

We will use this accumulating evidence to argue in favor of the need to deeply revise the way we conceptualize the emergence of human sensory brain organization as well as the way we assume such organization can be modified across the lifespan (see Table 1 for a summary of the assumptions and predictions of this proposal and their convergence/divergence from the classic CPs theory). Specifically, we suggest that plasticity and learning leading to the emergence of brain specializations (as well as to the outcomes of sensory recovery) across the lifespan should be conceptualized as reversible gradients: even though brain plasticity spontaneously decreases with age, it can be reversible in many cases, at any time across the lifespan, if the right technology/training/intervention is provided, even without any exposure to unisensory-specific experiences early in life due to full or partial sensory deprivations (Table 1).

2. Loosening the unisensory constraints on the emergence of anatomically-consistent brain specializations

Almost two decades ago, an influential work showed using functional Magnetic Resonance Imaging (fMRI), that the lateral occipital complex (LOC) in the ventral visual stream of the sighted brain, known to be activated by visual object recognition, was also activated by tactile object recognition (Amedi et al., 2001). Specifically, results showed that when participants were performing an object recognition task either in vision or touch, the whole-brain peak of activations was in LOC for both sensory modalities, thus in an anatomically consistent location across participants for both vision and touch. This raised the intriguing hypothesis that LOC specialization might be related to the processing of sensory-independent 3D geometric shapes rendering, rather than related solely to visual object recognition (this was later corroborated by many studies, e.g. see (Kassuba et al., 2014; Kim and Zatorre, 2011; Kim and James, 2010; Reed et al., 2004; Stilla and Sathian, 2008; Tal and Amedi, 2009; Zhang et al., 2004). This hypothesis was further strengthen by results demonstrating LOC activations for tactile or auditory objects recognition in congenitally blind adults, namely people who did not experience any visual inputs during CPs (Amedi et al., 2010; Dormal et al., 2018; Peelen et al., 2014; Pietrini et al., 2004) (Fig. 1). These results then challenged the classic CPs assumption positing that unisensory-specific experiences (vision in this case) are the key drive to the emergence of sensory specializations. Moreover, these results suggested that "visual" cortical regions could be activated by specific sensory-independent computations (e.g., LOC

activations for sensory-independent 3D objects-shape analyses) rather than by sensory-specific inputs as classically conceived (LOC activations driven by visual object recognition). But do these results extend to other "visual" regions or is this only a property of LOC? For instance, seminal studies in congenitally blind Braille readers documented extensive, widespread visual activations across most of the deprived visual cortex when reading Braille (Cohen et al., 1997; Sadato et al., 1998, 1996). But which are the properties of such recruitment? Will Braille-reading trigger specializations in the visual cortex consistently across participants? And will such activations closely resemble typical "visual" specializations reported for reading via the visual modality (e.g., similarly to the aforementioned results reported for LOC)? Or will Braille-reading simply trigger reading-specific specializations in the somatosensory cortex (consistently or non-consistently across individuals)? Our lab, in collaboration with the Dehaene, Cohen and Szwed labs, directly investigated this question in congenitally blind adults and we showed that when reading Braille, the whole-brain peak of activation in the congenitally blind brain was located in the visual Word Form Area (vWFA) in the ventral visual stream, a region previously known to respond only to letters presented visually in the sighted brain (Cohen et al., 2000) -from now on we refer to it as Word From Area (WFA). Importantly, similarly to LOC results, we also found that WFA activations were very consistent in their anatomical locations across congenitally blind participants, ultimately resulting indistinguishable to the locations of the activations in the same cortical region obtained in visual readers (Reich et al., 2011). Note that more recent evidence documented, using TMS, the causal role of WFA during Braille reading even in the sighted brain (Siuda-Krzywicka et al., 2016), further suggesting that such organization characterizes -at least to a certain extent- also the sighted brain (Fig. 1).

Over the years, similar results were reported by several additional studies documenting in congenitally blind adults, maintained specializations for other computations typically processed in the dorsal "visual" stream - also previously conceived as strictly visual. This was the case of spatial localization in the Middle Occipital Gyrus (MOG) and motion detection in the MT + complex, experienced via both audition or touch (Bedny et al., 2010; Collignon et al., 2011; Dormal et al., 2016; Jiang et al., 2014; Matteau et al., 2010; Poirier et al., 2006; Renier et al., 2010; Ricciardi et al., 2007; Strnad et al., 2013; Wolbers et al., 2011) (see also (Hagen et al., 2002; Rezk et al., 2020) for convergent results in sighted adults) (Fig. 1).

Taken together, all these results show that what were always described as strictly visual regions, could surprisingly still maintain their specializations in anatomically consistent locations, and in turn perform their typical computations via non-visual sensory inputs, even if their typical sensory input (i.e., vision) was never experienced across the lifespan. However, these results cannot exclude that what drives the emergence of such typical specializations in the blind brain is the fact that atypical pairings between a given computation (e.g., 3D objects shape analyses) and a given sensory modality (e.g., touch) were established during critical/sesnitive periods. Indeed, blind adults recognized objects through touch or spatially localize objects through audition across their whole life, or learned to read via Braille at the same age than sighted peers usually learned to read via vision, crucially learning such atypical pairings early in life. In other words, such computation-selective activations might be the result of specific plastic modifications occurring in the blind brain during infancy, when the brain is particularly plastic, to overcome the lack of vision. Thus, these results loosen the assumptions on the unisensory-specific nature of brain specializations, but do not exclude that a link between a given computation and a unisensory input (either typical or atypical) must be established early in life during critical periods in order for typical specializations to emerge.

Fig. 1. Classic unisensory (CU) versus computation-based (CB) cortical organization. This figure is a pictorial comprehensive overview of the available evidence for Task-Selective Sensory-Independent (TSSI) recruitments in humans. Lateral and ventral views of the human brain are depicted. Each icon represents a sensory brain region which showed maintained activations for its typical computation (e.g., spatial localization, spatial layout, 3D geometric shape analyses, etc.) via an atypical sensory modality, as opposed to classic unisensory-specific specializations. We reported in bold computation-based activations (CB) for which the underlying sensory-independent function is already well defined. We reported in italic, the computation-based activations (CB) for which the underlying sensory-independent function needs to be further refined. Anatomical locations are only an approximation. In the lateral view, activations are collapsed across hemispheres. In the legend to the figure, we report all icons, the sensory-region each icon represents, with the references to the papers that documented TSSI activations in that region and in parenthesis, next to each reference, the atypical sensory modality that was used in each study: A = audition; T = touch; SSD = Sensory-Substitution Device. For MT+, LOC, WFA and the fronto-temporal language network we only reported selected references of the most influential works reporting TSSI results. Note that for TSSI regions in temporal cortices, we also added references for TSSI recruitment coming from deaf animals -these regions are not depicted on the human brain. The figure is re-adapted from (Amedi et al., 2017).

2.1. Computation-based sensory-independent cortical organization

A crucial question that the aforementioned studies could not answer was: to what extent can we teach our brain to "see" via other sensory modalities across the lifespan, if vision was never experienced?

To answer this question, several labs, including ours, turn to a family of devices called Sensory-Substitution Devices (SSDs). SSDs are devices that aim at conveying information typically delivered via one

sensory-modality (e.g., vision) via a different sensory modality (audition; touch) using algorithms that can be learned by the users through specific training programs (Abboud et al., 2014; Bach-y-Rita et al., 2003; Meijer, 1992a,b). Specifically, visual SSD algorithms convey whole-visual scene information through manipulations of specific auditory or tactile features, ultimately successfully conveying the shapes and locations of objects (Bach-y-Rita, 2004; Meijer, 1992a,b) and even their colors (Abboud et al., 2014). It was shown that training with SSDs is effective in teaching blind users to perform a variety of 'visual' tasks, such as recognition of many different objects' types and their localization (Bach-y-Rita, 2004; ; Bach-y-Rita and Kercel, 2003; Netzer et al., 2019; Proulx et al., 2008; Striem-Amit et al., 2012a; Ward and Meijer, 2010), as well as for navigation in real and virtual environments (Brown et al., 2011; Chebat et al., 2015; Kolarik et al., 2017; Lobo et al., 2018; Maidenbaum et al., 2016), among many other tasks (Maidenbaum et al., 2014; Ward and Meijer, 2010).

SSDs are generally described as promising tools for visual rehabilitation keeping in mind their intrinsic limitations related to the much lower spatial resolution than vision (i.e., thousands rather than millions of pixels), much lower temporal resolution in the range of seconds rather than milliseconds, and demanding cognitive training required to properly learn to interpret SSD inputs (Maidenbaum and Amedi, 2019; Proulx et al., 2015).

Here, however, we will describe how the use of SSDs provide a unique and wonderful opportunity to further investigate the principles underlying the emergence of brain specializations, ultimately further examining the constraints imposed by unisensory experiences during critical periods. Indeed, through tailored SSD-training, one can establish in adulthood a new pairing between a given computation and an atypical sensory-modality which never processed that type of information before (e.g., perceiving body shapes through auditory SSD inputs). Then, when SSD users become familiar with this new sense-computation pairing, namely following dedicated training, it is possible to test with neuroimaging methods such as fMRI, which brain regions become active in the users' brain in response to SSD stimulations. Through this approach, we showed the maintenance of the large-scale "visual" cortex division between ventral and dorsal streams in the congenitally blind brain after 2 h of visual-to-auditory SSD training (Striem-Amit et al., 2012b). In addition, we created a longer SSD training program for congenitally blind adults lasting 70 h where we trained many of the known "visual" categories processed in the ventral visual stream, i.e., everyday objects, body-shapes, letters, numbers (Striem-Amit et al., 2012a) and more recently even faces (Arbel et al., 2020). Very interestingly, we found that in the congenitally blind brain, all the trained SSD visual categories recruited the region in the ventral visual cortex that in the sighted brain was known to process the same category of stimuli through vision. Specifically, we showed that object recognition via a visual-to-auditory SSD recruited LOC with high anatomically consistency across groups of participants, namely sighted, congenitally blind and late blind adults (Amedi et al., 2007; Ptito et al., 2012). In other words, these results documented maintained computation-selectivity for geometric shape analyses in LOC triggered by a sensory modality (audition) that conveyed this information for the first time during adulthood, namely well after the closure of CPs (note that some of our participants were tested way into adulthood, even at 50 or 60 years of age). This in turn further confirms that LOC is specialized in sensory-independent 3D geometric shape analyses rather than visual object recognition as classically described (Fig. 1). We showed similar results after SSD specific trainings also for body-shapes in the Extrastriate Body Area (EBA (Striem-Amit and Amedi, 2014)). More specifically, we showed that when congenitally blind participants perceived body-shapes and postures via auditory SSD, their whole-brain peak of activation (also at the individual level) was located in EBA, in an anatomical location indistinguishable from the individual peaks of activation elicited in sighted participants performing the same task in vision (Striem-Amit and Amedi, 2014). These results suggest that EBA is

specialized in sensory-independent body-shape analyses rather than visual body images processing as classically described (Fig. 1). Convergent results were obtained for SSD perceived letters in WFA (Sigalov et al., 2016; Striem-Amit et al., 2012a) as well as for SSD perceived numbers in the Number Form Area (NFA (Abboud et al., 2015). These results further confirm that WFA is specialized in sensory-independent symbol-to-phoneme conversion, rather than visual letter recognition. Similarly, they suggest that NFA is specialized in sensory-independent symbol-to-quantity conversion rather than visual number identification (Fig. 1). Importantly, we also showed that EBA, WFA and NFA in the blind brain were functionally connected to other main regions forming the typical network of processing for body-shapes (Striem-Amit and Amedi, 2014), letters, and numbers (Abboud et al., 2015), respectively. Finally, most recently, we reported similar results also for SSD perceived faces in the Fusiform Face Area (FFA) ((Arbel et al., 2020) see also (Murty et al., 2020) for converging results obtained in touch). We showed that after ~12 h of face dedicated training, blind-from-birth adults expert SSD users, recruited a region in the Fusiform Gyrus in an anatomical location compatible with FFA (both at the group and at the individual levels), alongside other regions known to be involved in face processing such as the Occipital Face Area (OFA). This suggests that FFA is specialized in sensory-independent face-shapes analyses, rather than visual face recognition (Fig. 1). We also recently showed that V6, a classically known dorsal stream region, keeps responding to navigation-related inputs in both congenitally blind and sighted blindfolded adults. Specifically, we showed that after short training with a minimalistic auditory SSD both groups of participants activated V6 during virtual maze auditory navigation (Maidenbaum et al., 2018) (Fig. 1).

Thus, these SSD studies highlighted that the emergence of specializations in occipital cortices is not constrained to any unisensory-experiences (either typical such as vision or atypical such as audition or touch) during early infancy. On the contrary, these studies suggested that "visual" specializations could emerge at any time across the lifespan even without any exposure to visual inputs during CPs, if one manages to convey the specific computation that a given 'visual' area is specialized in, via another sensory-modality using tailored technologies and related training. This of course does not mean that unisensory-specific inputs such as vision are unnecessary during CPs. Indeed, these data do not argue against the fact that in the case of occipital cortices, vision is the optimal sensory modality to promote the emergence of occipital specializations. Instead, what these data suggest is that vision is not irreversibly and critically needed and that such specializations can be still largely achieved via the remaining sensory modalities even during adulthood. These results in turn, strongly strengthen the conclusion that early unisensory-inputs' experiences are not the key drive to the emergence of sensory brain specializations. In addition, note that the training to which SSD users were exposed to was relatively short (i.e., a few hours hours rather than years of the proper unisensory-specific experiences during infancy). This unravels that sensory cortices maintain, across the lifespan, a previously unconceivable degree of flexibility for what it concerns the sensory modality activating them, while maintaining a strict preference to process a specific task/computation. These notions carry crucial insights also for sensory recovery, ultimately suggesting that it might be possible to recover sensory specializations in a brain that never experienced unisensory-specific inputs during CPs (see section 3).

Taken together, these results further strengthen evidence supporting the proposal that the emergence of specializations in visual cortices is driven by specific sensory-independent computations rather than by specific unisensory-inputs (i.e., vision) as classically conceived. We call this type of organization Task-Selective and Sensory-Independent (TSSI (Amedi et al., 2017; Heimler et al., 2015) and Fig. 1).

Based on all these results, we recently proposed that TSSI organization arises from a combination of two non-mutually exclusive principles: 1) sensitivity to task-distinctive features that is invariant to the input sensory modality (e.g., symbol-to-phoneme conversion in WFA

independently of the sensory modality used as input), and 2) the preservation of large-scale anatomical and functional (partly innate?) connectivity patterns (e.g., the connections between WFA and the rest of the reading network) (Amedi et al., 2017; Hannagan et al., 2015; Heimler et al., 2015).

Note that recently, evidence in favor of TSSI organization has been accumulating also for the deprived auditory cortices in deaf adults ((Benetti et al., 2017; Bola et al., 2017; Bottari et al., 2014) Fig. 1) (see for seminal works documenting recruitment of the fronto-temporal language network by sign-language in deaf native signers (Emmorey et al., 2007; MacSweeney et al., 2002; Neville et al., 1998; Nishimura et al., 1999; Petitto et al., 2000) and for converging results on deaf animals (Lomber et al., 2010; Meredith et al., 2011) Fig. 1). These results suggest that TSSI organization is a principle driving the organization of sensory cortices at large, thus beyond the 'visual' brain (Amedi et al., 2017).

2.2. Does TSSI organization extend to deprived primary sensory cortices as well?

Unfortunately, data regarding the extent to which TSSI organization extends to primary sensory cortices are still scarce and not conclusive (for a review see (Heimler et al., 2015)). One of the reasons behind the disparity of findings between primary sensory and higher-order cortices is that while there were clear hypotheses regarding the properties of TSSI recruitment in category-selective regions of higher-order sensory cortices, the hypotheses related to TSSI organization in primary sensory cortices appeared weaker. Indeed, primary sensory cortices are the first relay of sensory information in the cerebral cortex and are known to compute basic analyses of sensory features. Thus, among all cortical regions, they are considered the most unisensory-specific. What sensory-independent and task-selective computation could they perform if deprived of their natural sensory inputs? We suggest here a novel framework to investigate whether TSSI organization can emerge in early sensory regions: instead of searching for specific sensory-independent and low-level computations, one may focus on the main and large-scale organizational principle of primary sensory cortices, namely topographic mapping (e.g., retinotopy or tonotopy for visual and auditory primary sensory cortices respectively) (see also (Heimler and Amedi, 2020)). Is topographic mapping, or at least broad topographic division, maintained in the deprived primary sensory cortices? Very interestingly, recent studies demonstrated the maintenance of the large-scale functional connectivity patterns characterizing retinotopic and tonotopic biases in the congenitally blind (Striem-Amit et al., 2015) and congenitally deaf (Striem-Amit et al., 2016) respectively. However, so far, the functional meaning of these preserved anatomical connections remains largely unknown. A recent study, however, reported preserved retinotopic-like mapping in the deprived V1 of expert blind echolocators, especially in its anterior portion, typically termed 'peripheral V1' (Norman and Thaler, 2019) (Fig. 1). Echolocation is the ability to perceive space through sound echoes, e.g., by producing mouth-clicks and listening to the returning echoes (Griffin, 1944). Due to the difficulty of the training needed to properly master this technique, it is used only by a minority of blind people on a regular basis to perceive the space around them (Thaler et al., 2011). Specifically, the authors found that maps for sound eccentricity in expert echolocators were comparable to those for visual eccentricity in sighted people, especially for non-foveal eccentricities. They also showed that the degree of similarity between visual and auditory retinotopic-like mappings was positively correlated with the echolocation abilities (Norman and Thaler, 2019). These results suggest that retinotopic-like organization can arise, at least to some extent, even with atypical sensory inputs (audition in this case). This, in turn, suggests that also early visual regions seem to show the potential to be TSSI organized, thus similarly to higher-order sensory regions. These findings also highlight the crucial role of specific task-oriented trainings in order for TSSI properties to emerge. Indeed,

only blind expert echolocators showed retinotopic-like maps in response to spatial sounds, while such maps were not present neither in blind non-echolocators nor in sighted controls (Norman and Thaler, 2019). This latter study, then, carries crucial theoretical implications. However, it does not end the discussion on the re-organizational properties of deprived early visual regions, as the retinotopic-like mapping the authors reported extended mainly to deprived anterior (peripheral) V1. Even more importantly, the majority of congenitally blind adults are not echolocators and did not show at all preserved retinotopic-like mappings in their life-long deprived early visual regions. Indeed, any other result showing cross-modal recruitment of the deprived early sensory cortices, and mainly of the deprived early visual cortices, ever hinted at any preserved functional topographic maps. As a matter of fact, accumulating evidence suggests 'task-switching', in the deprived primary visual cortex, towards higher cognitive functions such as language, verbal and episodic memory or numerical cognition (Amedi et al., 2004, 2003; Bedny, 2017; Bedny et al., 2011; Burton et al., 2012; Kanjlia et al., 2016; Raz et al., 2005; Röder et al., 2002; Watkins et al., 2012), focused attention (Weaver and Stevens, 2007) and executive control (Loiotile and Bedny, 2018). These results may suggest that there might be two mechanisms at place in the (re)-organization following complete visual deprivation: (a) pluripotent task-switching plasticity taking place in deprived early visual areas, whereby these regions completely change the type of computations they respond to, thus showing their ability to process a variety of different computations -hence the pluripotency (Bedny, 2017); and (b) TSSI organization taking place in deprived higher-order visual regions, whereby these regions maintain their typical computations even if triggered by atypical sensory inputs. Indeed, pluripotent task-switching results are generally described as dramatically diverging from the predictions of TSSI brain organization. This is because language, memory, numerical cognition, attention or executive controls do not typically recruit early visual areas in sighted individuals (but see (Vetter et al., 2014)), are cognitive rather than sensory functions and are not organized topographically. However, we speculate that these results might not entirely diverge from TSSI predictions. Specifically, if one overcomes the classic assumption postulating that early sensory regions are highly sensory-specific in nature and they strictly process low-level sensory inputs, one can try to conceptualize topographic biases as task/computation-selective sensory-independent biases. More concretely, for example, the known eccentricity bias characterizing classic retinotopic mapping might be conceptualized as a task-selective sensory-independent high vs. low shape resolution bias. This would predict for instance, the activation of foveally responsive regions for Braille reading or face processing (i.e., tasks requiring high-resolution shape analyses) in the deprived primary visual cortex (Amedi et al., 2017; Heimler and Amedi, 2020). Or the activation of peripherally responsive regions during navigation tasks (Maidenbaum et al., 2018), or during auditory localization tasks (i.e., tasks requiring low-resolution shape analyses) (Fig. 1). In accordance with this latter prediction, a recent study reported preserved decoding of environmental sounds (thus another computation requiring low-resolution shape analyses) in the early visual cortices (including V1) of congenitally blind individuals, with maximal decoding accuracy in peripheral eccentricity regions (Vetter et al., 2020) (Fig. 1). Note that a similar result in response to sounds was also reported for the sighted population using the same sounds (Vetter et al., 2014). Such higher sound decoding accuracy in peripheral regions of early visual cortex in both populations is in line with previous evidence documenting that, relative to foveal regions, the periphery has richer connections with numerous non-visual areas, particularly with higher-level auditory areas and multisensory regions in the temporal and the parietal lobes (Beer et al., 2011; Eckert et al., 2008; Falchier et al., 2002; Rockland and Ojima, 2003). These results indicate that at least some of these connections might be preserved and functional, even in the lifelong absence of vision.

In light of this initial encouraging evidence, we speculate that

functional topographic biases might emerge in the deprived visual cortices independently of the sensory-input used, with the constraint that the information provided carries core sensory-independent 'retinotopic' features (see also (Heimler and Amedi, 2020)).

Even though, currently, evidence supporting these conclusions are still quite preliminary and mainly lacking for foveal V1, initial support for these predictions comes from the results obtained in the case-study of patient S who experienced severe visual acuity reduction due to corneal opacification from the age of six (Cheung et al., 2009). Using fMRI, the authors observed that in patient S classic foveally-driven regions were recruited by Braille letters, while classic peripherally-responsive regions were active during visual processing (Cheung et al., 2009). Given the low acuity of vision in patient S, this case-study suggests, in line with our hypothesis, that the eccentricity bias may indeed be fully conceptualized as a sensory-independent high vs. low shape resolution bias and that its core computations might be preserved in the absence of visual inputs. However, these results were obtained in one participant only, who underwent normal visual development during critical periods. Future studies may further investigate these intriguing questions in congenitally blind/deaf participants. Such works would unravel whether the whole brain is organized in a sensory-independent and task-selective manner, or if alternatively, there are indeed some constraints in the human brain regarding the nature of brain specializations, which depend on the specific sensory inputs available across the lifespan and/or during infancy.

2.3. How do such atypical sensory inputs reach the deprived visual cortices?

The main open question concerns the way atypical sensory inputs (e.g., auditory SSD information) reach the deprived sensory cortices. There is now accumulating evidence documenting that higher-order association cortices as well as low-level and even primary sensory cortices receive multisensory inputs (for reviews (Driver and Noesselt, 2008; Meredith and Lomber, 2017; Murray et al., 2016; Schroeder and Foxe, 2005; Stein and Stanford, 2008)). The underlying anatomical pathways of these cross-modal inputs include thalamo-cortical (from thalamus to cortex) and cortico-cortical (intracortical) connections (Budinger and Scheich, 2009; Henschke et al., 2015; Sperdin et al., 2009). However, when it comes to experience-dependent plasticity in the visual system, as discussed here, seminal evidence suggest that learning during critical periods and adult plasticity are both mediated exclusively by cortical mechanisms (Gilbert and Wiesel, 1992). And indeed, initial evidence with congenitally blind adults seems to support this conclusion, by suggesting that TSSI/cross-modal recruitment of visual areas is mediated by direct connections between visual and auditory cortices (Collignon et al., 2013; Klinge et al., 2010; Sigalov et al., 2016) or anyhow mediated by cortico-cortical connections (Bedny, 2017; Deen et al., 2015; Heine et al., 2015). Additional evidence in favor of the conclusion that experience-dependent plasticity is mediated only by cortical mechanisms comes from several anatomical studies on the congenitally and early blind populations reporting microstructural changes and even atrophy in the subcortical projections connecting to the occipital cortex (Noppeney et al., 2005; Pan et al., 2007; Park et al., 2007; Reislev et al., 2017; Shimony et al., 2005). Also, the size of LGN was shown to be reduced in blind compared to sighted adults (Cecchetti et al., 2016). Contrary to this conclusion, however, several evidence in blind rodents documented enhanced anatomical connections between auditory sub-cortical structures and the deprived visual cortices (Bronchti et al., 1989; Chabot et al., 2008; Rhoades et al., 1985), as well as altered connections in LGN due to experience-dependent modifications (Jaepel et al., 2017; Rose and Bonhoeffer, 2018; Sommeijer et al., 2017). Finally, a recent study in congenitally blind humans suggested the mediation of the posterior thalamus in visual cortex activations elicited by somatosensory processing (Muller et al., 2019). These results, in turn, suggest that cross-modal inputs may reach the visual cortex also through feedforward thalamo-cortical projections and not only through cortico-cortical ones.

Taken together, the aforementioned results highlight that there is still much work to be done in order to fully understand the pathway(s) through which atypical sensory inputs reach deprived sensory regions. Future studies could further characterize the involvement of thalamo-cortical projections to cross-modal recruitment of deprived sensory cortices. Furthermore, they could investigate the extent to which thalamo-cortical and cortico-cortical pathways carry to the deprived visual cortices the same type of atypical sensory inputs or whether there are some differences between the two pathways based on tasks/computations and/or input sensory modalities.

3. Should we retire the concept of unisensory-specific critical periods in favor of the concept of reversible plasticity gradient?

One of the main issues which arose from the aforementioned studies investigating the properties of brain organization in sensory deprived populations and especially in congenitally blind SSD users, concerns the nature of critical periods of development as conceived classically (Hensch, 2004; Knudsen, 2004) (see Table 1 for direct comparisons between the classic theory on critical periods and our revised proposal). Indeed, all SSDs studies highlighted that the pairing between a given sensory-modality and a given computation does not need to be established during critical periods of development for the related typical brain specializations to emerge (Abboud et al., 2015; Amedi et al., 2007; Arbel et al., 2020; Striem-Amit et al., 2012a; Striem-Amit and Amedi, 2014) (see section 2.1 for details). Then, does it mean that unisensory-specific experiences during critical periods do not play any role in the emergence of brain specializations?

We do not argue against the fact that early experiences in life play an important role for the emergence of typical cortical development. As a matter of fact, we fully agree with the notion that the development of our sensory systems is indeed subordinate to a plasticity gradient which decreases with age (i.e., the brain ability to learn and to modify cortical connections/activations as a consequence of learning). We also agree with the notion that certain sensory modalities are more suited than others to carry out specific tasks/computations. And indeed, because of this, under typical developmental conditions, we all end up with similar sensory brain specializations (Table 1).

However, studies with sensory deprived populations – especially those involving SSDs technologies- seriously challenge the notion that unisensory-specific experiences during critical periods are the key drive for the emergence of sensory specializations (Knudsen, 2004). We argue that they highlight, instead, that typical specializations can be triggered by any sensory modality, at any point during the lifespan, even without any unisensory-specific experience early in life, if the atypical sensory input (e.g., auditory rather than visual) can properly convey the underlying computation of a given cortical region. More specifically, SSD studies with congenitally blind adults unraveled that, if a computation-oriented training is provided, even for a short amount of time and during adulthood/across the lifespan, it can drive any sensory input carrying such computation-selective information, to recruit a given TSSI region in the "visual" cortex, alongside its related network of processing (Abboud et al., 2015; Striem-Amit and Amedi, 2014).

Taken together, SSD studies reviewed here suggest that there might be an organizational principle driving sensory brain specializations that is deeper than unisensory-preference, namely a hard-wired predisposition to process specific sensory-independent computations in specific brain regions, -rather than an organization mainly driven by hard-wired sensory-specific regions as classically conceived. We suggest that such computation-oriented predispositions arise from the unique interactions between the two proposed principles determining the emergence of human sensory brain organization: 1) sensory-independent and computations-specific properties in sensory regions and 2) preserved connectivity patterns (Amedi et al., 2017; Heimler et al., 2015).

Based on these results, one can predict that via specific and

individually tailored training programs, we can reverse our existing plasticity gradient at any time point across the lifespan, independently of the unisensory-specific inputs experienced during critical periods. This would mean, for instance, that if we train an adult person on a computation that s/he did not experience during critical periods, s/he will nonetheless recruit the corresponding TSSI specialized region anatomically consistently across individuals -see for instance, work from The Dehaene lab for initial encouraging results with illiterate adults recruiting WFA when learning to read during adulthood, namely well after the closure of critical/sensitive periods (Dehaene et al., 2015) (Table 1).

Crucially, similar predictions can be extended also to sensory recovery. Specifically, we can predict that if we train an adult person who just recovered a sense, in a computation typically carried out by the newly reafferented sense, s/he will activate typical brain regions for its processing. In other words, based on all the TSSI results reviewed above (sections 2 and 2.1), we propose that it is possible to recover sensory specializations, at any time point across the lifespan, if training focused on specific computations is provided. We also further suggest that a multisensory training approach where the newly restored sensory modality is paired with a familiar and spared one, might be especially effective (see also (Heimler et al., 2015, 2014; Heimler and Amedi, 2020)). In this context, SSDs can be promising tools to complement the newly restored sensory-input (Heimler et al., 2015). Let's take the case of visual restoration as an explanatory example of our proposed approach. We propose that candidates for sight restoration might use SSDs prior to the intervention, and learn, for example, to perceive SSD-presented body-shapes, ultimately recruiting the EBA and its related network of processing (Striem-Amit and Amedi, 2014) (i.e., TSSI recruitment). Then, after surgical sight restoration, the SSD stimulation can be paired with visual input, mediating two types of benefits. The familiar SSD input can help to better understand the newly-restored visual input. For example, simultaneously presenting a body shapes both through an SSD and through vision may help the patient to perceive fine details of the image or bind visual features into a coherent shape. Moreover, by exploiting the TSSI properties of higher-order visual cortices, such pairing may facilitate a neural network's adaptability, and thus allow reafferented visual cortices to efficiently process their typical sensory input. For instance, in the case of body shapes, it has been shown that SSD-presented body shapes recruit the EBA in a TSSI manner, and that this region is functionally connected to other regions typically involved in body shape processing in the blind population (Striem-Amit and Amedi, 2014). Given the documented sensory-flexibility of TSSI cortical regions, pairing auditory SSD inputs to vision when perceiving body-shapes may aid the visual cortex, and specifically the EBA and its related network, to tune towards its typical visual inputs. A similar logic can be applied to basically all the known visual categories and perhaps even for more low-level computations (see section 3.1), and more generally to the whole sensory brain, beyond "visual" cortices. Evidence directly supporting this proposal are still lacking in the sight restoration literature. Available evidence, instead, report lack of recovery for category-selective specializations in restored visual patients who were not exposed to visual inputs during CPs, mostly cataract recovered patients, also after years of sight recovery (Bottari et al., 2018, 2016; Fine et al., 2003; Grady et al., 2014; Lewis and Maurer, 2005; Roder et al., 2013). However, no study today tried to implement specific computation-oriented (multisensory) trainings on these patients to track the extent to which such trainings might aid the (re)-establishment of typical cortical recruitment by the restored visual input, in line with the predictions of the reversible plasticity gradient (RPG) (Table 1) and TSSI organization (see sections 2 and 2.1). Note that similar conclusions have been also reached in the literature related to auditory recovery after cochlear implantation, namely the most established invasive procedure for sensory restoration (Gaylor et al., 2013). Specifically, studies with early (pre-lingual) deaf individuals receiving cochlear implants (CIs) after the closure of CPs showed that

the auditory recovery of these patients, especially for spoken language, was very poor (Kral, 2013), albeit these patients still retained traceable plastic changes in cortical responses (Kral et al., 2019; Schorr et al., 2005). Importantly, though, late-deaf individuals receiving CIs showed great natural spoken language recovery after implantation (Lazard et al., 2012). Furthermore, initial and accumulating evidence in both deaf humans and animals with CIs, starts to corroborate the predictions of the RPG and TSSI cortical organization, namely, that computation-oriented (multisensory) trainings indeed support the (re)-establishment of typical cortical recruitment by the restored sensory input, independently from the exposure to unisensory-specific experiences during CPs (Table 1). For instance, exposure to audio-visual language rehabilitative training (speech-reading therapy, pairing sign language with spoken language) was shown to substantially improve auditory linguistic recovery compared to auditory-only training in CI patients (Heimler et al., 2014; Heming and Brown, 2005; Lyness et al., 2013; Strelnikov et al., 2015, 2013). Furthermore, a study on early deaf ferrets receiving bilateral CIs during adulthood, showed that in these animals, an audio-visual training aimed at recovering auditory localization skills, namely a computation to which these animals were not exposed to during CPs, was far more effective than a unisensory, auditory one both at the neural and the behavioral level (Isaiah et al., 2014). Convergent results on the benefit of multisensory stimulations were also recently reported in the healthy population experiencing vocoded speech (i.e., degraded speech simulating the signal delivered by the CI) embedded in speech-like noise (Cieśla et al., 2019). In this recent study, we showed immediate improvement in speech understanding when degraded auditory signal was paired with vibratory signal conveying certain speech features (i.e., fundamental frequencies (Hollien and Shipp, 1972)) via a custom-built auditory-to-vibration SSD (Cieśla et al., 2019) (Fig. 2). These results in turn, strengthens the prediction that the combination of a familiar modality (e.g., vision/vibration) with a novel, newly restored one (e.g., audition) during task-oriented training programs, can be a powerful way to restore efficient and task-specific sensory recovery, even in case of interventions occurring in adulthood.

To summarize, we here posit that if a person aims to learn a new pairing between a sense and a given computation after the closure of critical periods, tailored (multisensory) computation-oriented training is necessary in order to elicit brain activations organized in a TSSI fashion. If such supervised training is not provided, typical brain specializations may not (re)- emerge (Bedny et al., 2010; Collignon et al., 2013; Grady et al., 2014; Roder et al., 2013) (see Table 1) -but see (Gandhi et al., 2017; Ostrovsky et al., 2006) for data hinting to the possibility that typical specializations in higher-order sensory regions might recover after the closure of critical periods also through natural exploration of the environment, namely without supervised training.

Note that we do not claim that plasticity/learning mechanisms leading to TSSI organization do not vary across the lifespan (e.g., the pattern and nature of synaptic connections leading to learning). Unfortunately, systematic empirical work on lifespan differences in behavioral and neural manifestations of plasticity and learning is notoriously difficult to conduct, and thus still scarce, with many of its mechanisms still unknown (Lindenberger and Lövdén, 2019; Ziegler et al., 2019). However, it is known that from childhood to adulthood there are profound changes both in structural and functional connectivity which affect cognitive development and, in turn, most probably influence learning mechanisms (Lindenberger and Lövdén, 2019; Tang et al., 2017; Uhlhaas et al., 2010). In other words, this line of works suggests that the neural context for learning a new skill is modified by age, and these changes may affect plasticity at the local level, ultimately resulting in different neural circuits responsible for learning at different stages across the lifespan (Lindenberger and Lövdén, 2019).

Therefore, what we propose based on SSD results, is that even though the mechanisms of learning might differ across the lifespan, the
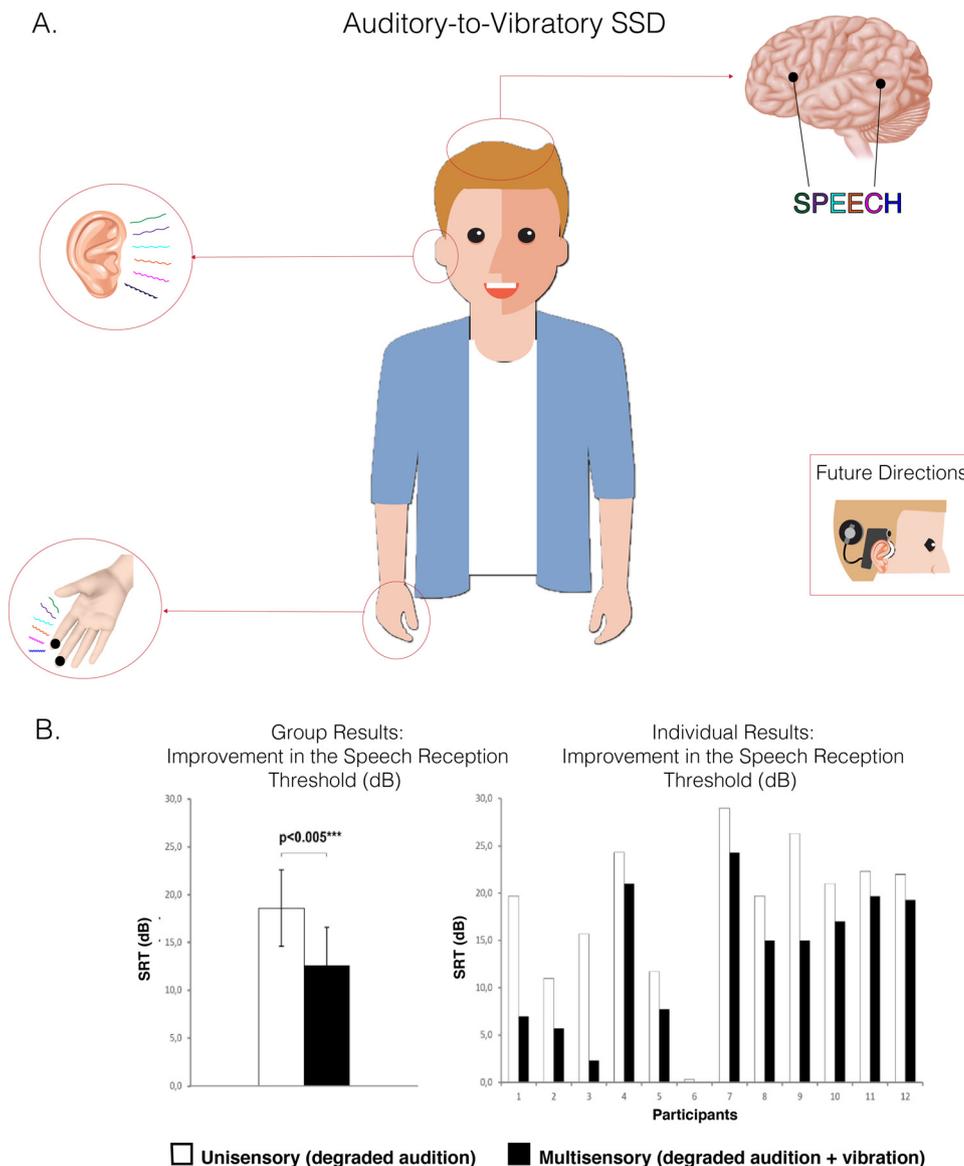
Fig. 2. Benefits of multisensory SSD training on performance. Speech understanding in noise. **A.** In-house audio-to-touch SSD transforms fundamental frequencies contained in speech (Hollien and Shipp, 1972) into corresponding vibratory frequencies delivered on the fingers, potentially activating the language brain network. **B.** Results (Ciesla et al., 2019). SSD vibration-audition pairing immediately improved the understanding of degraded speech without any specific training. A clear improvement in speech understanding both at the group level (left panel) as well as at the individual level, can be observed in all (hearing) participants. Note that in both graphs Speech Reception Threshold values are reported (SRT(dB) – Signal-to-noise-ratio between speech and noise that allows for 50 % speech understanding), thus lower values indicate an improvement. Based on the many finding documenting TSSI organization in higher-order sensory cortices, we suggest that such multisensory pairing may facilitate/strengthen the recruitment of the language network, ultimately improving performance. We aim at testing cochlear implant (see inset) using the same approach.

final outcome of such learning can still be similar, namely the emergence of typical brain specializations -at least in higher-order sensory regions. However, we argue that in most cases, for these typical brain specializations to emerge in adulthood, a (multisensory) computation-specific training is preferable.

3.1. Does the concept of reversible plasticity gradient extend also to early sensory regions?

When the assumptions and predictions related to the proposal of the reversible plasticity gradient (RPG) are extended to early visual cortices, conclusions appear less straightforward. First, available evidence documents deficient low-level visual processing in sight restored adult patients (Dormal et al., 2015; Fine et al., 2003; Levin et al., 2010; Lewis and Maurer, 2005; Maurer et al., 2006; Ostrovsky et al., 2006). In addition, we also reviewed evidence documenting that in blind adults, early visual cortices switch their functions in favor of processing higher-order cognitive functions (Amedi et al., 2004, 2003; Bedny, 2017) see section 2.2). Studies assessing how this documented pluripotent task-switching plasticity affects visual recovery are still lacking, thus we cannot exclude that such type of cross-modal recruitment might prevent the reafferented early visual cortex to typically regain its functionalities

(but see encouraging results in deaf cats (Land et al., 2016)). Overall, this suggests that at least to a certain extent, there might be a detrimental effect on visual recovery due to the lack of visual-specific experiences early in life, a conclusion that would be in line with classic theories of critical periods (see also (Ishikawa et al., 2014)). However, some studies suggest that also this aspect might be reversible. Intriguingly, recent evidence with animal models indicate that chemical interventions can release molecular 'breaks' of plasticity (involving the balance between inhibition and excitation within sensory networks) and trigger the reversion of the plasticity gradient, ultimately resetting juvenile brain plasticity and increasing sensitivity to external inputs (Deidda et al., 2015; Duffy and Mitchell, 2013; Hensch and Quinlan, 2018; Kral, 2013; Morishita and Hensch, 2008; Takesian et al., 2018; Takesian and Hensch, 2013). Treatment based on this approach is being piloted for amblyopia (Davis et al., 2015; Sengpiel, 2014; Vetencourt et al., 2008), where endogenous permissive neuromodulators are modified to induce plasticity in adults who have had monocular visual deprivation. Evidence are starting to emerge in support of promoting plasticity in these patients non-invasively through the occlusion of the amblyopic eye, which was shown to homeostatically boost responses in the deprived eye (Lunghi et al., 2015). A recent study suggests that non-invasive interventions in adult amblyopic patients are even more

successful when pairing the occlusion of the amblyopic eye with physical exercises (Lunghi et al., 2019) (Table 1). Improvements in both visual acuity and stereopsis extended up to 1 year after the end of the treatment (Lunghi et al., 2019) (and see (Hensch and Quinlan, 2018) for a similar proposal stemming from animals results). The benefit of physical exercise seems related to the fact that it induces a further decrease in GABAergic inhibition in the primary visual cortex, which adds to the decrease in GABAergic inhibition exerted by the occlusion of the amblyopic eye (Lunghi et al., 2015), ultimately increasingly facilitating visual cortex activity and plasticity (Fu et al., 2015; Stryker, 2014). Should these approaches show further confirmations, they may be expanded to people recovering from binocular deprivation, e.g. blindness. In this case, the maintenance of the macro-structural topographic organization of V1 (Bock et al., 2014; Striem-Amit et al., 2015), and perhaps also of its core computations (see section 2.2 and (Cheung et al., 2009; Norman and Thaler, 2019; Vetter et al., 2020)), along with rejuvenating/facilitating its ability to wire and refine its connections once visual input is restored, may facilitate an efficient takeover of the reafferented early visual cortex. Unfortunately, studies testing the effect of multisensory training on the recovery of low-level visual functions and processing are still not conclusive, but encouraging evidence with partially deprived animals and even humans (i.e., in cases of hemianopia) are starting to emerge (Bolognini et al., 2005; Dakos et al., 2020; Dundon et al., 2015a, 2015b; Frassinetti et al., 2005; Jiang et al., 2020, 2015; Leo et al., 2008; Stein and Rowland, 2020). Specifically, a series of recent studies showed that hemianopia in adult cats could be entirely reverted by multisensory audio-visual trainings aimed at improving the orienting behaviors of the animals towards the lesioned hemifield. Post-treatment results showed an almost complete recovery of orienting behaviors to visual stimuli in the hemianopic field (Dakos et al., 2020; Jiang et al., 2020, 2015; Stein and Rowland, 2020). These results suggest that multisensory trainings might be effective to restore typical specializations also for low-level visual functions and prompt for additional studies in this direction also in humans and in individuals recovering from full blindness. In this respect, note that very intriguingly, studies with congenitally blind SSD users document that via SSDs, blind people can perform acuity tests above the legal score for blindness (Chebat et al., 2007; Levy-Tzedek et al., 2014; Sampaio et al., 2001; Striem-Amit et al., 2012c). This suggests that in cases of visual restoration, SSDs can be paired with vision to facilitate also the conveying of low-level visual features (see section 3 for the results on multisensory trainings in the (re)-establishment of higher-order sensory specializations). This prompts future studies to systematically investigate the effects of (multisensory) trainings on sensory recovery also for low-level sensory features and how such trainings interact with techniques involving the release of molecular 'breaks' of plasticity for reversing the plasticity gradient -Note, however, that initial evidence from recovered cataract patients suggest that certain low-level visual functions such as visual acuity or contrast sensitivity can recover to a large extent, at least behaviorally, also through natural exploration of the environment, i.e., without dedicated training (Ganesh et al., 2014; Kalia et al., 2014).

Finally, we would like to suggest that another, novel approach to test the role of critical periods for the emergence of brain specializations without studying sensory deprived/restored people, can be to provide healthy adults with novel sensory experiences (NSEs). This means experiences to which the brain has never been exposed to, neither during critical periods of the specific user nor during the entire history of human evolution. In animals models, NSEs were successfully elicited invasively (Hartmann et al., 2016; Thomson et al., 2017, 2013).In humans, however, we must find a way to convey NSEs noninvasively via our existing sensory channels, thus making SSDs perfect tools for this approach. Examples of such experiences can be infrared (IR) vision conveyed through sound or ultrasound perception through touch. Initial evidence confirms that NSEs can be induced in humans via SSDs (Kaspar et al., 2014; König et al., 2016; Negen et al., 2018).

The intriguing following question is whether after NSE-oriented trainings, the adult human brain can develop dedicated specializations to process these computations, and whether such specializations would be consistent across individuals, namely, for the processing of information beyond our natural senses. Future studies may shed further light on the role of critical periods early in life, as well as on the mechanisms driving our brain organizations and on mechanisms of learning and plasticity across the lifespan.

4. Conclusions

We reviewed here a wealth of studies mainly with sensory deprived populations and in particular with congenitally blind sensory-substitution users, all suggesting that sensory brain organization is driven by specific sensory-independent computations rather than by unisensory-specific inputs as classically conceived. We provided evidence suggesting that such organization is also characterizing the typically developing brain (i.e. in people that did receive typical sensory inputs during CPs). Evidence in this direction is so far more conclusive for higher-order sensory regions, but evidence in favor of this conclusion for early sensory cortices is also starting to emerge. We propose that all these results prompt for a revision of the classic assumptions positing a crucial role of unisensory-specific critical periods in the emergence of sensory brain specializations. Specifically, we do not argue against the existence of a natural plasticity gradient embedded in our brain which is maximal at birth. However, we suggest, based on this growing body of work, that such gradient may be reversed at any time across the lifespan, independently of the exposure to unisensory-specific experiences early in life -if one manages to convey the typical computation of a given region via dedicated stimulations. We indeed reviewed data in sensory restored individuals suggesting that such reversion could take place both via invasive approaches such as chemical interventions involving the release of molecular 'breaks' of plasticity, and/or via computation-oriented trainings relying on intact natural sensory-modalities or on novel technologies (e.g., sensory-substitution) across the lifespan. Taken together these results not only hold great promise for more successful rehabilitation procedures aimed at sensory recovery during adulthood, but they also provide a unique window into the organizations principles of brain specializations and their flexibility and stability mechanisms across the lifespan.

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