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Editorial

The sensory-deprived brain as a unique tool to understand brain development and function

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On October 11th-13th 2018, the second edition of "The Blind Brain Workshop" was held in Lucca (Italy), which gathered most among the leading worldwide experts in the study of the sensory-deprived brain. The aim of the workshop was to tackle, from multiple and different perspectives, the current conceptual and methodological challenges on the topic and to understand how perceptual experience sculpts the brain during development, as well as in adulthood.

Altogether, the contributions of this three-day workshop emphasized that the current understanding of the structural and functional organization as well as the development of the brain has significantly been promoted by the studies on the consequences of sensory-deprivation both in humans and animals. Nevertheless, by providing a unique opportunity for a direct comparison of different sensory-deprivation models, the workshop has uncovered open aspects in blindness, deafness and even somatosensory deprivation research. Suggestions for a substantial rethinking were postulated. The event additionally highlighted the role of early sensory experiences for functional development. In particular, the research on sensory-restoration has provided first evidence for the role of experience in typical development of different neural systems.

The increasing interest about the sensory-deprived model in humans

The sensory-deprived brain has always represented a theme of curiosity for the understanding of human cognition and behavior. Although blindness and deafness have been inspiring art, narrative, philosophy, anthropology and even religion (e.g., https://www.britannica.com/topic/history-of-the-blind-1996241#ref322884), only recently sensory deprivation in humans became the object of extensive neuroscientific investigation.

In particular, from the mid '90s, the advent of methodologies for the *in vivo* structural and functional exploration of the human brain - including positron emission tomography (PET), functional magnetic resonance imaging (fMRI), high-resolution electroencephalography and magnetoencephalography (M/EEG) and non-invasive brain stimulation (such as transcranial magnetic stimulation, TMS) -, led to a significant expansion in the number of studies in this field. To this purpose, surveys of indexed literature searches on PubMed Central (PMC) for experimental studies on either blindness or deafness, using different neuroimaging/stimulation approaches, revealed a total of more than 500 articles published since 1992 (Figure 1a, b). Undoubtedly, similarly to other research topics dragged by the neuroimaging impetus, the number of studies addressing the functional and structural neuroanatomy in congenital, early or late blind and deaf humans has been constantly and significantly increasing over time (Figure 1a, b). The initial 'gold rush' that assessed brain metabolism and neural plasticity in the sensory-deprived brain (just to cite a few pioneering studies, such as Cohen et al., 1999; De Volder et al., 1997; Sadato et al., 1996; Veraart et al., 1990; Wanet-Defalque et al., 1988) has then led to more and more sophisticated questions that investigate the general principles governing the functional organization of human brain (e.g. Benetti et al., 2017; Bola et al., 2017; Bridge et al., 2009; Handjaras et al., 2016; Kupers et al., 2011; van Ackeren et al., 2017).

Still referring to the literature surveys (Figure 1a,b), studies on structural changes following sensory deprivation have started with the advent of analytical tools (e.g., voxel-based morphometry - Ashburner and Friston, 2000) to perform voxel-wise comparisons of gray matter between sensory-deprived and control subjects (Andelin et al., 2018; Fine and Park, 2018; Jiang et al., 2009) and since then continued at a constant pace including white matter and subcortical structures (Anurova et al., 2019; Cecchetti et al., 2016b; Shu et al., 2009). Since the preliminary observations, two aspects clearly emerged. First, studies consistently showed that the whole brain, and not just the deafferented cortical and subcortical structures, as well as their constitutive white matter tracts, undergoes a substantial reorganization (Fine and Park, 2018; Voss, 2019). At the same time, though, as structural analyses were primarily performed on limited samples, whose demographic and clinical variables (e.g., residual light perception, cause of blindness, education, time of blindness onset, prematurity, etc.) were heterogeneous, discrepancies were reported among studies. Consequently, more recently, researchers are beginning to share brain structural data to replicate previous observations in larger sample sizes (e.g. Cecchetti et al., 2016b) and to enhance the possibility to covariate the data with crucial anamnestic and etiological characteristics (Bridge et al., 2009; Li et al., 2017; Siuda-Krzywicka et al., 2016).

To complete our overview, electromagnetic measurements, including the use of M/EEG as tools for electrical neuroimaging (Michel and Murray, 2012), inferred crucial information regarding the spectro-temporal dynamics of brain responses in sensory-deprived cortex (Ioannides et al., 2013; Schepers et al., 2012). Interestingly, the population of study characterized, to some extent, the method of interest: a significant higher application of M/EEG has been adopted for the study of deafness as compared to blindness (see Figure 1b) and, for compatibility reasons, EEG has been the primary method of investigation in the context of auditory restoration via cochlear implants. On the contrary, non-invasive brain stimulation approaches, such as TMS (transcranial magnetic stimulation), are restricted to blindness (Figure 1a), likely because experimental modulations of occipital visual areas are relatively more feasible than of auditory cortex (e.g. Rossi et al., 2009; Sandrini et al., 2011).

Characterizing functional (re)organization in the sensory deprived brain

The early brain imaging work in sensory-deprived individuals has focused on the cross-modal reorganization of sensory areas (e.g., in early visual and auditory areas in blind and deaf individuals, respectively). It was impressive to observe a highly reliable activation within the sensory-deprived cortical areas. Nonetheless, the behavioral outcome, the functional significance and the anatomical substrates of these changes still remain unclear and are subjected to a wide debate that even questions their truly compensatory and functional-specific nature. Which is the exact topography of cross-modality in deprived sensory areas? How does cross-modal input reach the reorganized region(s)? Is this reorganization truly compensatory? Which information, task, or function can actually go cross-modal? Is cross-modal activity specific for the sensory deprived brain?

The burgeoning literature on this topic reveals that the effects of sensory deprivation vary enormously depending on the selected brain function, the specific experimental setup, the type of the deprivation, or the timing of the loss (Bedny et al., 2010; Collignon et al., 2013; Frasnelli et al., 2011; Kim et al., 2017). Despite such heterogeneity, milestones that attract a general consensus and still pave the road for the research to come, characterize the existing literature. In the '80s, the first evidence about the activation of visual cortex in blind individuals (Phelps et al., 1981; Veraart et al., 1990; Wanet-Defalque et al., 1988) questioned the functionality of this area in individuals born without sight and, on a more general perspective, the degree of neuroplasticity of sensory areas. Subsequent studies supported the notion that the early visual cortex in blind individuals is activated in a task-related manner (Rosler et al., 1993; Sadato et al., 1996; Sadato et al., 1998; Uhl et al., 1991), while observations in brain damaged patients (Hamilton et al., 2000), as well as data from brain stimulation, confirmed that the blind 'visual' cortex may be causally linked to non-visual tasks (Amedi et al., 2004; Cohen et al., 1997; Hamilton and Pascual-Leone, 1998). On this line, convincing evidence revealed cross-modal responses within the auditory cortex in deaf individuals as well (e.g. (Fine, 2005; Finney et al., 2001). Moreover, subsequent observations revealed that even higher-level cognitive tasks are associated to cross-modal responses in the deprived visual cortex (e.g., verb generation: Amedi et al., 2004; language processing: Bedny et al., 2011; Noppeney et al., 2003; Roder et al., 2002a; spatial navigation: Kupers et al., 2010) or auditory cortex (e.g. memory functions: Cardin et al., 2013), thus questioning the degree of spatial and functional specificity of cross-modal responses in early 'visual' areas (e.g. Burton et al., 2002; Stevens et al., 2007) (see for a review Bedny, 2017; Singh et al., 2018; Röder and Neville, 2003).

In addition, the age at which a sense is lost has a pivotal role in modulating neuroplasticity, as demonstrated, for instance, by the extent of cross-modal recruitment within occipital areas in case of late blindness (e.g., Bedny et al., 2010; Collignon et al., 2013), or by the different degree of behavioral compensations in relation to the age of sensory loss (Wan et al., 2010)(Röder and Rösler, 2003). As described below, these considerations serve as a *memento* on how significant for brain development are both the time and the exposure to uni-/cross-modal inputs, as emphasized by various contributions in this Special Issue.

Looking at the sensory-deprived brain the other way around

The study of the sensory-deprived brain is at the same time a unique tool to understand to what extent a specific sensory modality is truly a mandatory prerequisite for the brain morphological and functional architecture to develop and function. Initial functional studies in people with no vision reported overlapping activations in higher-level cognitive regions with sighted individuals (De Volder et al., 2001; Roder et al., 2002b; Ross et al., 2003; Weeks et al., 2000). Nonetheless, only the demonstration that congenitally blind individuals during non-visual object recognition show topographically-organized category-related patterns of neural response in the ventral "visual" pathway indicated that visual experience is not necessary for the brain to develop a certain functional organization (Pietrini et al., 2004). Moreover, the brain appears to be able to process specific types of information independently from the modality that carries the input (Pietrini et al., 2004).

Subsequent research from multiple labs confirmed an overall preservation of the large-scale functional organization of congenitally blind individual brain across several functional domains (Benetti et al., 2017; Bonino et al., 2015; Bonino et al., 2008; Collignon et al., 2011; Holig et al., 2014; Mahon et al., 2009; Ptito et al., 2009; Ricciardi et al., 2009; Ricciardi et al., 2007; Striem-Amit et al., 2016; Striem-Amit et al., 2012b). These findings have acted as a strong leverage prompting the emergence of partially overlapping perspectives about the principles governing neural plasticity in absence of a sensory modality and about brain functional organization, such as metamodality (Pascual-Leone et al., 2001), supramodality (Pietrini et al., 2004; Ricciardi et al., 2014; Ricciardi and Pietrini, 2011), functional selectivity hypothesis (Dormal and Collignon, 2011), amodality (Striem-Amit et al., 2018) or sensory-independent task selectivity (Amedi et al., 2017). Altogether, beyond the different semantic terms, the above definitions agree that the morphological and functional large-scale architecture of the human brain results to be - to a significant extent - modality invariant. This, in turn, implies that the human brain is somewhat pre-programmed to develop and function in the way it does (Ricciardi et al., 2014). Nonetheless, several questions still remain open: which task/information can be sensory-independent? How is unimodal information integrated into more abstract representations? Do overlapping functional responses imply identical mental representations between sensory-deprived and typically developed individuals?

While often thought as mutually-exclusive explanations, modality-independent responses and cross-modal plasticity might likely represent coexisting or interacting aspects of the same reorganization phenomenon in the sensory-deprived brain (Amedi et al., 2017; Cecchetti et al., 2016a). Should our 'rethinking' indeed begin by overcoming this theoretical dichotomy, looking more at the homologies and the dissimilarities across different models of sensory deprivation, and favoring a stronger dialogue between multisensory research in typically developing samples and sensory-deprived individuals?

Restoring sensory input

As depicted in Figure 1, research on sensory restoration is much less frequent than in permanently sensory deprived humans. While people with treatable blindness are rare, deaf people who have received cochlear implants are more numerous, as it is reflected by the number of available studies.

The reorganization following sensory loss, in particular in blindness from birth, has often been interpreted as an adaptative mechanism. Thus, it must be wondered whether such an adaptation is beneficial or of disadvantage for sensory recovery. As a matter of fact, people treated for congenital dense bilateral cataracts are known to suffer multiple sensory impairments even many years after surgery. It has been suggested that the functions which develop late recover the least (Maurer et al., 2007) and that the more complex a visual function, the less recovery is expected (McKyton et al., 2015). However, there are functions as well which recover astonishing well, such as perception of biological motion (Bottari et al., 2015; Hadad et al., 2012) and face detection (Gandhi et al., 2017). Uncoverying the neural mechanisms which explain why some functions recover better than others will provide insights about the neural basis of sensitive phase plasticity. Moreover, how the restored sense is linked to the remaining senses has hardly been investigated (Putzar et al., 2007), though it seems crucial for promoting recovery.

As a result of the advancements in treating sensory defects (e.g., corneal and stem-cell transplantation, gene therapy, retinal prosthesis etc.), new sight restoration approaches are currently being developed to treat degenerative retinal disorders which typically cause late blindness (e.g., retinitis pigmentosa). Sight recovery in humans implanted with retinal prosthesis is, to date, quite limited (Humayun et al., 2012; Rizzo et al., 2014); however, the visual system seems to reveal some recovery following intensive use of the implants (Castaldi et al., 2016).

While bionic devices for sight recovery are far from being ready to become a widely used clinical tool, auditory restoration trough cochlear implants (CI) represents a clinical routine for deaf individuals, and the number of individuals who received a CI worldwide had reached 324,000 by the end of 2012 (https://www.nidcd.nih.gov/health/cochlear-implants). These numbers easily explain why the model of auditory restoration represents the major source for research on sensory re-afferentation (see Figure 1d). Similar to sight restoration, a robust body of evidence indicates that the age at implantation plays a crucial role for the degree of auditory recovery: in case of bilateral congenital profound deafness, CI surgery has been recommended to be done within the first two years of life (Kral and Sharma, 2012); indeed, after the age of 6 years, very poor restoration outcomes have been reported (Govaerts et al., 2002; Niparko et al., 2010). In fact, early sensory restoration may favor auditory functions to develop within their corresponding sensitive periods and, at the same time, prevent the documented deterioration or functional disconnection of auditory structures (Kral and Sharma, 2012).

In case of untreatable sensory defects, alternative means of sensory enrichment have to be considered. In particular, there has been a long tradition on sensory substitution (SSD, e.g. Bach-y-Rita et al., 1969; Proulx et al., 2014; Striem-Amit et al., 2012a), that is to convey information accessible only by the deprived modality via non-deprived sensory channels. Current sensory-substitution devices still require long periods of training and are only able to reproduce parts of the lost sensory input. However, functional brain imaging studies have shown that the sensory input provided through SSDs is processed in a task-specific manner and typically relies on the same brain regions that would have selectively processed that “specific visual information” (see Cecchetti et al., 2016a; Striem-Amit et al., 2012a).

Where are we going?

Investigating adaptation to sensory deprivation and recovery of neurocognitive functions following sensory restitution provides a unique opportunity in humans to understand the experience dependence and independence of brain development, the mechanisms of developmental vs. adult neuroplasticity and the unique contribution of the individual senses for brain functioning. The results achieved so far and those expected from future research will greatly contribute to unveil the interaction of genes and experience for brain development. Moreover, research in sensory deprived individuals will allow us to improve neurorehabilitation of people with sensory impairments and thus their life quality.

During the Blind Brain Workshop 2018, several options to further improve collaboration in research were discussed. First, the promotion of data sharing initiatives and multisite protocols will be fundamental to overcome the problem of underpowered study designs genuine to research with rare populations. Data sharing will promote coordinated, ambitious collaborative projects with more standardized study protocols and analysis pipelines. Second, protocols to report detailed characteristics of sensory deprived individuals would not only help clarifying inconsistent findings across labs but would additionally help to understand and predict different individual outcomes. Finally, we encourage the challenging but promising enterprise to run experimental sensory deprivation studies in healthy adult humans, since they allow a much higher control and standardization than possible when studying natural cases of sensory deprivation.

This Special Issue

This Special Issue ‘*Rethinking the sensory deprived brain: Novel perspectives from the Blind Brain Workshop 2018*’ intends to offer a comprehensive and up to date overview of the experimental neuroscientific research on sensory deprivation. Contributions from the Blind Brain Workshop 2018 lecturers are clustered into three sections - ‘*The blind brain to understand the physiological functional and structural organization of the brain, and the other way around’, ‘What the deprivation model comparison provides for the understanding of neuroplasticity’ and ‘Sensory recovery and restoring’* -, each preceded by a commentary, which discusses the broader implications of the presented work and opinions by the individual contributions. Altogether, these review papers provide original perspectives on brain development, experience-dependent brain plasticity, sensory deprivation and restoration. Furthermore, new approaches for the study of the sensory-deprived brain, the comparison of models and of rehabilitative approaches (including neuroprostheses) after sensory loss are presented across the different sections to highlight the more general and translational outcomes of this line of research. Due to the demographic changes in most societies, sensory loss as a consequence of aging will become an emerging challenge, certainly a main topic for the next “The Blind Brain Workshop”.

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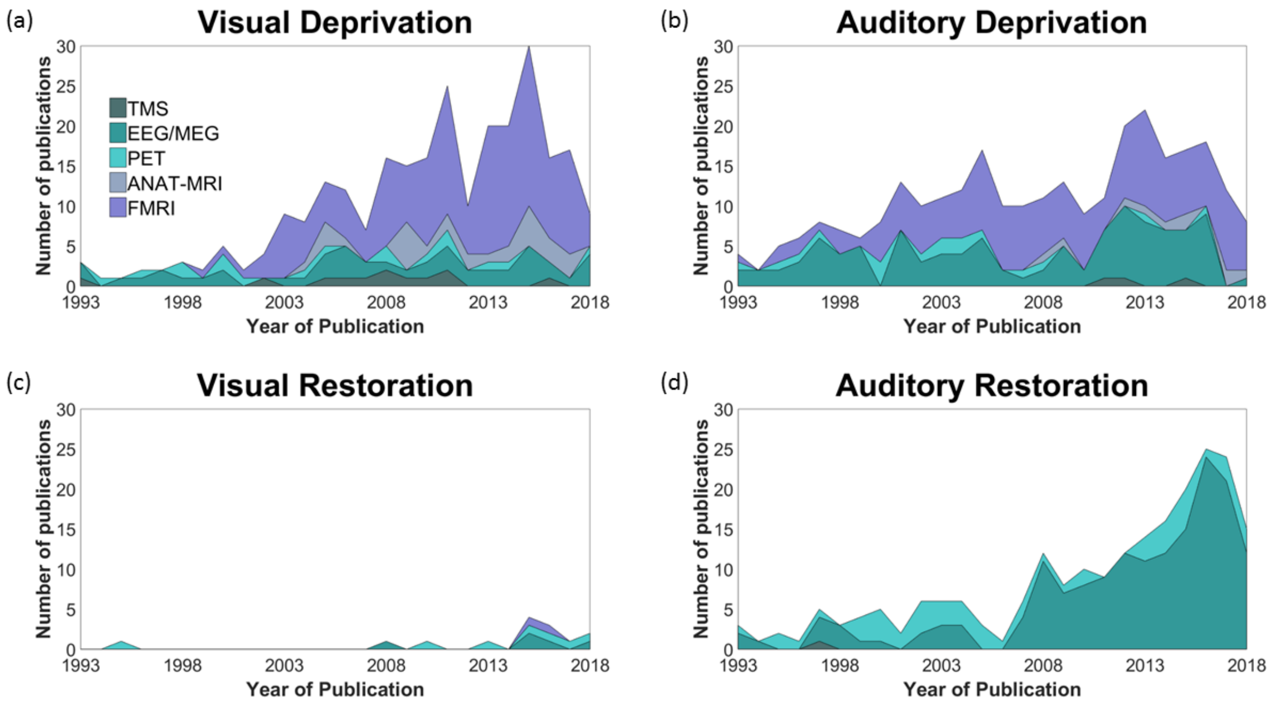

Figure 1. Number of indexed publications for each model of investigation and technique. Surveys of indexed literature were conducted on PubMed Central (PMC). Keywords combination comprised each model of interest (e.g. blindness or visual deprivation) and the method of study (TMS, EEG, MEG, PET, MRI or fMRI). Articles were screened to exclude unrelated publications.