Blindness has always fascinated artists (e.g. [23,25,33,34,37,74,75]), philosophers (e.g. [5,13,15]) (Figure 1), and also scientists (e.g. [2,6-8,39,50,52,54,57,59]). Blindness is defined as visual impairment presenting visual acuity worse than 3/60 (i.e. categories 4 to 6 of the WHO) [77]; neuroscience and psychology studies usually include only categories 5 (visual acuity worse than 1/6 with light perception) and 6 (no light perception). On the one hand, observing the behavior of a person who never had visual experience helps us to understand the role and importance of vision in acquiring knowledge about the world around us [6-8,29]. Contrasting the performance of sighted and blind people in a task testing a particular cognitive ability makes it possible to understand how this ability has been shaped in sighted people by their visual experience. On the other hand, studying the blind also helps to understand how they compensate for the lack of vision to adapt to their environment [50,52,54,57]. It is indeed a unique opportunity to investigate the plasticity of the brain and its ability to transfer certain cognitive skills from one modality to another in order for these skills to be used regardless of visual deprivation. One of the most striking examples is braille reading that gives access to written language through touch [54]. Indeed, the increased tactile abilities of blind people allow them to analyze and interact with their environment to do things that sighted people preferentially do by using vision, as if *they see with their hands* [13]. Another line of research on crossmodal plasticity in blindness focuses on how the development of certain cognitive skills occurs through the interaction between two or more sensory modalities. For instance, blind people show different topographical capacities to locate somatosensory stimuli applied on their body as compared to sighted people, suggesting that body representation usually develops through visuo-tactile interactions [29]. While the study of blindness has contributed substantially to improve psychological and neuroscientific knowledge about visuo-tactile interactions, there is however relatively little research focused on how visual deprivation impacts pain perception. Despite their small number, these studies show that blind people seem not to perceive pain in the same way as sighted people, which suggests the importance of vision for the processing of nociceptive information in the brain. It is indeed hypothesized that the adaptive role of nociception might depend on its ability to interact with other sensory modalities such as vision.

1. Early visual deprivation increases nociceptive sensitivity

In 1964, Zubek et al. [78] noticed that placing sighted participants in complete darkness for one week resulted in an increase in their sensitivity to heat and pain, as measured by means of warmth and pinprick pain thresholds. Most surprisingly, these effects lasted for several days after the termination of the visual deprivation period. Recent animal studies in mice however showed that one-week visual deprivation was not sufficient to impact perception of mechanical and thermal noxious stimuli [67]. Indeed, only mice deprived of vision for one month showed mechanical and thermal hypersensitivity similar to that of mice reared in complete darkness and anophthalmic mice, indicating that nociceptive hypersensitivity depends on visual deprivation duration [67]. People with blindness of peripheral origin that occurred within the first year of life have lower detection thresholds to heat and cold stimuli, as well as lower pain thresholds, as compared to sighted participants [61]. They perceive thermal stimuli of the same temperature as more painful than sighted people [60]. They also have better capacities to discriminate intensity changes during thermal stimulation [63] and they respond faster to nociceptive stimuli, but only those selectively conveyed by C fibers [62]. Importantly, nociception and pain perception does not seem impacted by blindness that occurred later in life [60], highlighting in sighted people the importance of early visual experience to detect nociceptive stimuli and perceive them as painful. The lack of change in sensitivity in late blind contrasts with Zubeck's data [78] and would suggest that short-term visual deprivation and longer-term deficits of the visual system impact the functioning of the nociceptive system through different mechanisms.

It was first suggested that changes in congenitally blind people in responding to nociceptive and painful stimuli could reflect an increased sensitivity due to brain plasticity [61]. Vision could play a modulatory effect on pain [35,36,40,41,69] (however see [66]) and authors hypothesized that the loss of a potential inhibitory effect of vision on pain at early steps of development would alter the connections between the cerebral regions involved in nociceptive processing, giving rise to nociceptive hypersensitivity. Secondly, nociceptive hypersensitivity in early blind people could reflect an adaptive attitude to deal with pain [39]. The aforementioned studies indeed reported that congenitally blind people are more attentive to pain signals in daily life, and that uncertainty about an impending potentially painful stimuli could make them more anxious, which would consequently increase pain [30,61]. This hypothesis is in accordance with a recent study showing that nociceptive

hypersensitivity in anophthalmic mice is associated with structural and functional changes of the amygdala, a brain structure involved in emotions [68]. Thirdly, we might hypothesize that early blind people have also developed a kind of hyperresponsiveness to threats to compensate the lack of vision in preventing contact of potentially noxious stimuli. Despite of the lack of clear evidence to support one of those hypotheses more specifically, they all illustrate that, since early visual deprivation affects nociceptive processing and pain perception, the ability to detect and react to noxious stimuli is shaped in sighted people by their early visual experience. However, without disregarding the possibility of the two former mechanisms presented here above, recent data, presented in the following paragraphs, attempt to corroborate the latter hypothesis, notably by studying the importance of the visual system in the ability to detect and locate noxious events [70,73].

2. Early visual deprivation changes the spatial representation of nociceptive stimuli

Correctly localizing pain is an important cognitive ability to optimize the defensive role of the nociceptive system. To adequately plan and guide defensive action toward threatening and potentially damaging stimuli, we must localize which part of the body has been hurt, but also, and most importantly, where the object that caused the injury is located [12,18]. Numerous neuropsychological studies have evidenced that the brain uses different cognitive abilities to map somatosensory information (e.g. [29]). The well-known somatotopic representation constitutes an anatomical map of the body surface based on the ordered projections of receptive fields to spatially organized groups of neurons [51]. Besides that, the spatiotopic representation considers the relative position of the body part on which the stimulus is applied (e.g., proprioception) [64], and, therefore, uses external space as reference frame. Such spatiotopic representation provides an appropriate readout for the brain to identify external objects in contact with the body, and therefore to spatially guide actions towards these objects [72]. This dual ability in mapping nociceptive inputs is evidenced by experiments showing that the perception of the location of nociceptive stimuli is substantially impacted in sighted people when an unusual and confusing posture is adopted by the body, such as when the hands are crossed over the body midline [9,56,70,73] (see [29,38,72] for similar effect for touch). Crossing the hands makes it indeed difficult to locate somatosensory stimuli since their anatomical position mismatches that of the stimulated hand in external

space (i.e., the left hand is placed in the right part of space and vice versa). While this effect was shown even when sighted participants were blindfolded, spatial judgements of nociceptive stimuli by congenitally blind people seem not impacted by body posture [70] (Figure 2), as if they would base their spatial perception of nociceptive stimuli mostly on their anatomical position. However, this does not exclude the possibility that they can take into account the relative position of their limbs in external space and rely on spatiotopic representation to locate somatosensory stimuli [58]. They are perfectly able to process spatial information from other sensory modalities, such as the position of auditory stimuli in external space [2,7] and create a map of their spatial environment [50,52]. It has indeed been suggested that the different somatosensory mapping abilities depend on a weighting process, which, in case of conflict, allows to select the most appropriate spatial code [1,58]. For example, when blind people are encouraged to judge the location of nociceptive stimuli according to a spatiotopic reference (i.e., "*where is the stimulus coming from?*"), they are just as confused as sighted people when their hands are crossed [73] (Figure 2). They are therefore able to use a spatiotopic reference frame but would have difficulties in inhibiting their *over-weighted* somatotopic representation in case of mismatch. In sighted people, the two types of representations would be activated with equivalent weights. These studies therefore show that the way the brain analyzes and uses nociceptive inputs to locate potential damage to the body, and probably the way it responds to them, is also patterned by vision. Interestingly, other studies showed that the spatial arrangement of the different limbs relatively to each other can modulate cortical responses to nociceptive stimuli [48] and, even more, the strength of reflexive defensive responses [55], suggesting that spatial cognition can not only significantly influence the processing of afferent information, but also the activity of descending pathways. The importance of early visual experiences is further demonstrated by data showing that this top-down influence on reflexes is observed in sighted and late blind, but not in early blind people [76].

3. Multisensory interaction between nociception and vision as a defensive function to protect the body

Being mapped according to spatiotopic coordinates allows nociceptive stimuli to interact with inputs from other modalities such as visual ones [11,21,70]. The brain is indeed

able to integrate somatic and extra-somatic inputs to build a multisensory representation of the body extended to its immediate surrounding, the so-called peripersonal space [14]. The representation of peripersonal space has first been described in electrophysiological animal studies [26]. These studies have indeed highlighted the existence of polymodal neurons, i.e., neurons responding to stimuli from different sensory modalities, particularly in the premotor area [53], the intraparietal sulcus [17], the superior parietal lobe (area 7b) [32] and the putamen [27] of the macaque brain. More precisely, these neurons associate a tactile receptive field (RF) covering a body part and a visual RF extending a few centimeters in the space around the same body part. Importantly, the visual RF is spatially locked to the tactile RF, following the limb on which it is anchored during its movements [26]. This would create a buffer zone allowing these neurons to be activated even before the contact of a stimulus on the skin. This neural organization would make it possible to establish a line of defense allowing the brain to detect and probably react to physical threats [14]. One study described similar neurons responding to both visual and thermo-nociceptive stimuli in monkey area 7b [16]. In humans, studies showed that the perception of nociceptive stimuli can be modified by the occurrence of external objects that are visually perceived near the body [10,20]. More precisely, it has been shown that nociceptive and visual stimuli interact with each other provided that the visual stimulus approaches or occurs in the close vicinity of the limb on which the nociceptive stimulus is applied [9-12,18,20,21,43,71]. Multisensory interaction implies that the perception of the stimulus of one sensory modality is modified by the stimulus of the other modality, and for nociception and vision this interaction has been shown in both directions (e.g. [11,18]). Visuo-nociceptive interactions are thought to contribute to the establishment of a defensive line that extends into the peripersonal space of our body. Peripersonal space is indeed often thought to contribute to the protection of the body by tracking surrounding stimuli in order to keep threatening objects away and prevent them from damaging the body [14]. The visual system is partially innately organized to detect potential threats [31] and predict collision with the body [24]. However, the role of peripersonal space would be more than foreseeing contacts of noxious stimuli with our body. Once contact has been made with these stimuli, visuo-nociceptive interactions would make it possible to optimize and finely tune protective actions (e.g. [3]), although data supporting a role of visuo-nociceptive interactions for the motor control of actions are still lacking today (see [22] for preliminary results).

Such intimate entanglement between pain and vision is also illustrated by other clinical data. Corollary to the fact that congenitally blind people perceive pain differently than sighted people, pathological pain can also impact visuospatial perceptual abilities. For example, complex regional pain syndrome can impair the perception of visual stimuli presented near the patient's pathological limb [4,19,28]. These cases constitute examples of a neuropsychological double dissociation supporting the considerable overlap between nociceptive and visual functions. The importance of multisensory interaction is further illustrated by congenital insensitivity to pain, often taken as an example demonstrating the important functional role of nociception: because of pain insensitivity, these patients cannot avoid serious injuries, which can jeopardize their survival. However, Sternbach pointed out that survival can be compromised when congenital insensitivity to pain is combined with other multiple difficulties such as neuropathies affecting other sensory systems [65]. Adults with congenital insensitivity to pain can indeed survive their childhood because they learned to rely on other sensory cues to deal with danger. In other words, the alarming and protective role of the nociceptive system will not solely depend on its functional integrity, but also on the brain's ability to integrate nociceptive inputs with other sensory inputs [49], such as visual inputs.

If vision and multisensory interaction seem important to efficiently support the protective role of nociception, this leads to the question of how blind people protect themselves. Do they cope with dangers less effectively? Do they expose themselves more often to injuries as some of the patients with congenital insensitivity to pain? Are they forced to learn about threatening objects solely based on their nociceptive experiences? It is worth noting that the nociceptive system can also be seen as a system patterned to prevent noxious contact. The aforementioned studies on blind people used laser-induced radiant heat stimuli [30,60-62,70,73], that is, stimuli that specifically activate cutaneous nociceptors without any contact with the participant's skin. Blind people can thus very well *estimate the proximity of fire to the degrees of heat* [15] before being burned. This allows to counter-argue the idea according to which, since usual daily-life contact with noxious objects also generates tactile inputs, multisensory interactions would take place essentially via the tactile system, whereas the nociceptive system would be ineffective for interaction due to its slow conduction velocity. Since the nociceptive system can detect radiant thermal threats (i.e. before their contact with

188 the body), we hypothesize that it can be perfectly adapted for multisensory interactions. The
189 brain has indeed the means to compensate for differences between the sensory modalities in
190 terms of conduction speed and distance of peripheral receptors [42]. Congenitally blind
191 people can probably also compensate visual deprivation with increased sensitivity to sound
192 locations (see discussion in [2,7]) to develop and map their peripersonal space [52]. Moreover,
193 they can use their expertise in manipulating a cane to explore their distant environment and
194 interact with out-of-reach objects (differing from sighted people who process distant stimuli
195 with vision, limiting touch for interaction with nearby objects). It was indeed shown that tools,
196 in addition to their use as means to optimize manipulation capacities such as strength and
197 handiness, can be used to extend our peripersonal space [44] and to translate stimulus
198 features that we usually perceive with vision into touch [45,46]. Blind people use the cane as
199 an extension of their arm to decode sensory patterns of an object through the vibrations
200 induced by its contact with the cane [59] (Figure 1), but also to detect distant potential danger
201 and prevent contact with physical threats. Sighted people also use tools to keep noxious
202 objects at distance while interacting with them. This is for instance the case of the poker we
203 use to manipulate embers in a fireplace: dexterity of manipulation comes from vibratory
204 feedbacks perceived along the rod while avoiding burns. In other words, by using tools we can
205 translate stimulus features that might eventually activate our nociceptors into tactile inputs.

206

207 **4. Conclusion**

208 Pain is often described as a percept resulting from the brain's interpretation of a
209 pattern of activities arising from different nerve fibers (see [47]). However, pattern theories
210 have mostly limited their investigation to the convergence of nociceptive inputs with other
211 somatosensory signals. The study of blindness shows that pain and other nociceptive
212 responses emerge from nervous processing mechanisms that integrate visual information.
213 Moreover, the experiments reviewed here show that the protective function of nociception
214 depends on its ability to interact with vision (and probably hearing and touch). Vision plays an
215 important role by (1) modulating the sensitivity of the nociceptive system and (2) by
216 integrating nociceptive inputs in a representation of the body extending in its surrounding
217 space, used as a defensive buffer zone.

Conflict of interest statement

The authors report no conflict of interest.

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Figure captions

Figure 1. Cultural representations of blindness. Top right image: detail of *The Parable of the Blind* by Pieter Bruegel the Elder (Museo di Capodimonte, Naples, Italy). Inspired by the Gospel of Matthew 15:14, the painting illustrates the metaphor *the blind leading the blind* which depicts the situation in which a person lacking in knowledge receives help or advice from someone else who does not know more. Ignorance is symbolized here by the supposed inability of the blind to orient themselves in space and cope with obstacles, in accordance with the idea that visual deprivation prevents adaptation [5] and knowledge [25]. Right image: illustration of the *Letter on the blind for the use of those who see* by Diderot [15] in which he reports his observations and conversations with a man born blind to support his theory that our ideas and knowledge are not inspired by God but derived from our perceptual experiences and shaped by the available senses. The letter also illustrates the Molyneux's problem, a thought exercise from empirical philosophy that addresses the question of how a person blind from birth who regains his sight would recognize objects that were previously identified by other senses such as touch. The image depicts a blind man crossing his canes originally featured in Descartes' *Dioptrics* [13]. Descartes illustrated the sensory substitution of vision by touch and the abilities of blind people to explore the objects in their environment by the tactile vibrations perceived through their rod. Crossing the rods, this blind person understands that what he feels in his left hand, for example, comes from an object in his right space. This idea of crossmodal plasticity was exemplified by the well-known fictional character Daredevil (bottom left image, Frank Miller (c) Marvel Comics). Indeed, contrary to popular ancient times ideas about disability and maladaptation, the blind person represented by Daredevil is able to substitute the loss of vision by over-developing the other senses so as to become a hero with extraordinary behaviors. For example, his auditory hyper-sensitivity (called his *radar sense*) allows him to precisely map his spatial environment so as to adequately face dangers (e.g., to avoid punches of his enemies and to finely adapt and spatially guide his own movements to their targets).

Figure 2. Nociceptive temporal order judgement (TOJ) tasks used to investigate spatial remapping of nociceptive inputs. A. Sighted (but blindfolded) and early blind (i.e., blind from birth or having lost sight during the first year) participants judged the temporal order between two laser-induced radiant heat stimuli, one applied on each hand at a temperature above the activation threshold of nociceptive Aδ fibers, with various time intervals between them. Participants reported which of the two stimuli they perceived as being applied first. Tasks were performed either with an uncrossed hand posture (blue), or with their upper limb crossed over their body midline (red) so that the left hand was in their right side of space, and vice versa. Task instruction encouraged participants to rely on one particular mapping reference frame. In a first condition they were asked to report which of their hands they perceived as stimulated first ("*which hand?*"), priming the use of somatotopic/anatomical reference frame. In a second condition they were asked to report from which side of space the stimulus they perceived as first was coming ("*which space?*"), priming the response from their spatiotopic reference frame. Performances of the sighted and early blind participants are illustrated in the graphs in B and C respectively. Performances are measured with sigmoids characterizing the probability of reporting one of the two stimuli as first perceived – here the left one – according to the different time intervals (or SOA for stimulus-onset asynchrony) (by convention negative values correspond to trials during which the left stimulus is presented first, the positive values those with the right stimulus presented first). These sigmoids are characterized, among other parameters, by their slopes indexing the uncertainty in the participants' responses. Typically, participants are more uncertain during the crossed hand posture (red sigmoids) as compared to the uncrossed posture (blue sigmoids), suggesting that their responses are affected by the conflict between the two reference frames during the crossed hand posture (i.e., the left hand is right-sided and the right hand left-sided). However, whereas this is observed under the two task instructions for sighted participants, early blind participants were only affected by body posture during the spatial instruction. When early blind participants had to respond which part of their body they perceived as stimulated first, they performed the task with their hands crossed as well as with their hands uncrossed. This suggests that in sighted participants the two reference frames are equally competing for spatial representation of the nociceptive inputs, while blind participants mostly rely on their somatotopic reference frame and succeed to inhibit the response of the spatiotopic representation when it is mismatching with the somatotopic one. Adapted from [73]