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Disengagement of attention with spatial neglect: A systematic review of behavioral and anatomical findings

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ABSTRACT

The present review examined the consequences of focal brain injury on spatial attention studied with cueing paradigms, with a particular focus on the disengagement deficit, which refers to the abnormal slowing of reactions following an ipsilesional cue. Our review supports the established notion that the disengagement deficit is a functional marker of spatial neglect and is particularly pronounced when elicited by peripheral cues. Recent research has revealed that this deficit critically depends on cues that have task-relevant characteristics or are associated with negative reinforcement. Attentional capture by task-relevant cues is contingent on damage to the right temporo-parietal junction (TPJ) and is modulated by functional connections between the TPJ and the right insular cortex. Furthermore, damage to the dorsal premotor or prefrontal cortex (dPMC/dPFC) reduces the effect of task-relevant cues. These findings support an interactive model of the disengagement deficit, involving the right TPJ, the insula, and the dPMC/dPFC. These interconnected regions play a crucial role in regulating and adapting spatial attention to changing intrinsic values of stimuli in the environment.

1. Introduction

Nearly 30 years ago Posner et al. (1984) published a clinical research paper that profoundly influenced our understanding of the parietal lobes' role in spatial attention. Building upon the first authors (Posner, 1980; Posner et al., 1982) conception of spatial attention as a manifestation of three independent processes – disengaging, moving and engaging attention – the authors evaluated the performance of patients with spatial neglect after focal left or right parietal damage with a spatial cueing paradigm. The study unveiled three primary findings: Firstly, when a contralesional target appeared shortly after a brief ipsilesional cue, reaction times (RTs) exhibited a disproportionate increase. The authors postulated that this RT increase was indicative of deficient disengagement of attention. This was because patients could covertly (i.e., without moving their eyes) shift their attention when both the cue and target appeared in the contralesional half of space. The specific deficit must therefore affect their ability to unlock, or disengage, attention from the ipsilateral cue. Secondly, a similar deficit was observed in a subset of patients when a central arrow pointing towards ipsilesional space preceded a contralesional target. Thirdly, even when entirely neutral cues that provided no directional information were presented at fixation, patients displayed significantly increased RTs to contralesional targets. Posner et al. (1984) concluded that the parietal lobes play a critical role in disengaging attention from the current location, and parietal damage, particularly to the superior parietal lobe, results in a disengagement deficit.

Posner et al.'s (1984) report inspired numerous subsequent studies, and by 2001, a meta-analytic review by Losier and Klein (2001) had identified 12 reports with data from patients with parietal damage using variations of the spatial cueing paradigm. In this work, we provide an update, expansion, and discussion of the review's conclusions, incorporating findings from studies published in the last two decades.

2. Literature search

In October 2023 we performed a comprehensive literature search across four databases, namely Pubmed, Web of Science, Embase, and Psychinfo. We employed the following search terms: 'spatial neglect' OR 'hemineglect' AND 'spatial attention' OR 'disengagement'. After screening and reading through the initial 3636 non-duplicate records, we retained a total of 66 studies for further analysis. Fig. 1 shows the PRISMA 2020 flow diagram.

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Among these 66 studies, 49 had been published subsequent to the meta-analysis performed by Losier and Klein (2001). These newer studies are the primary focus of our current review. Notably, 57 of the selected studies utilized variations of a spatial cueing paradigm, while the remaining nine studies employed alternative task types designed to measure dynamic aspects of spatial attention, such as the Flanker task. Although these alternative task types may not be directly comparable to the cueing paradigm, they offer valuable insights into processes related to attention disengagement and capture, hence meriting their inclusion in our discussion.

Within this review, we address the key topics that were originally discussed by Losier and Klein (2001), expanding upon them where necessary with fresh data. Utilizing data extracted from 12 distinct reports, Losier and Klein (2001) explored the contrasting impacts of exogenous versus endogenous cues, the consequences of left-versus-right hemisphere damage, and the nuanced modulation of cueing effects as a function of time or the anatomical and behavioral traits of patients with spatial neglect. Additionally, we introduce and examine questions that had not been previously addressed in their meta-analysis, such as the role of task relevance and the anatomical correlates of the disengagement deficit.

3. Definitions

Prior to delving into the findings of the studies identified in our literature search, it is imperative to establish the precise terminology that will be utilized throughout this paper. For clarity, we define the following key terms:

1. Field effect: Refers to the increase in RTs observed in the contralesional hemifield of patients with unilateral brain damage. It is often expressed as a difference score between contralesional and ipsilesional RTs.
2. Validity effect: Denotes the difference between RTs to targets shown subsequent to the presentation of invalid cues and those subsequent to valid cues. A positive validity effect signifies a discernible benefit

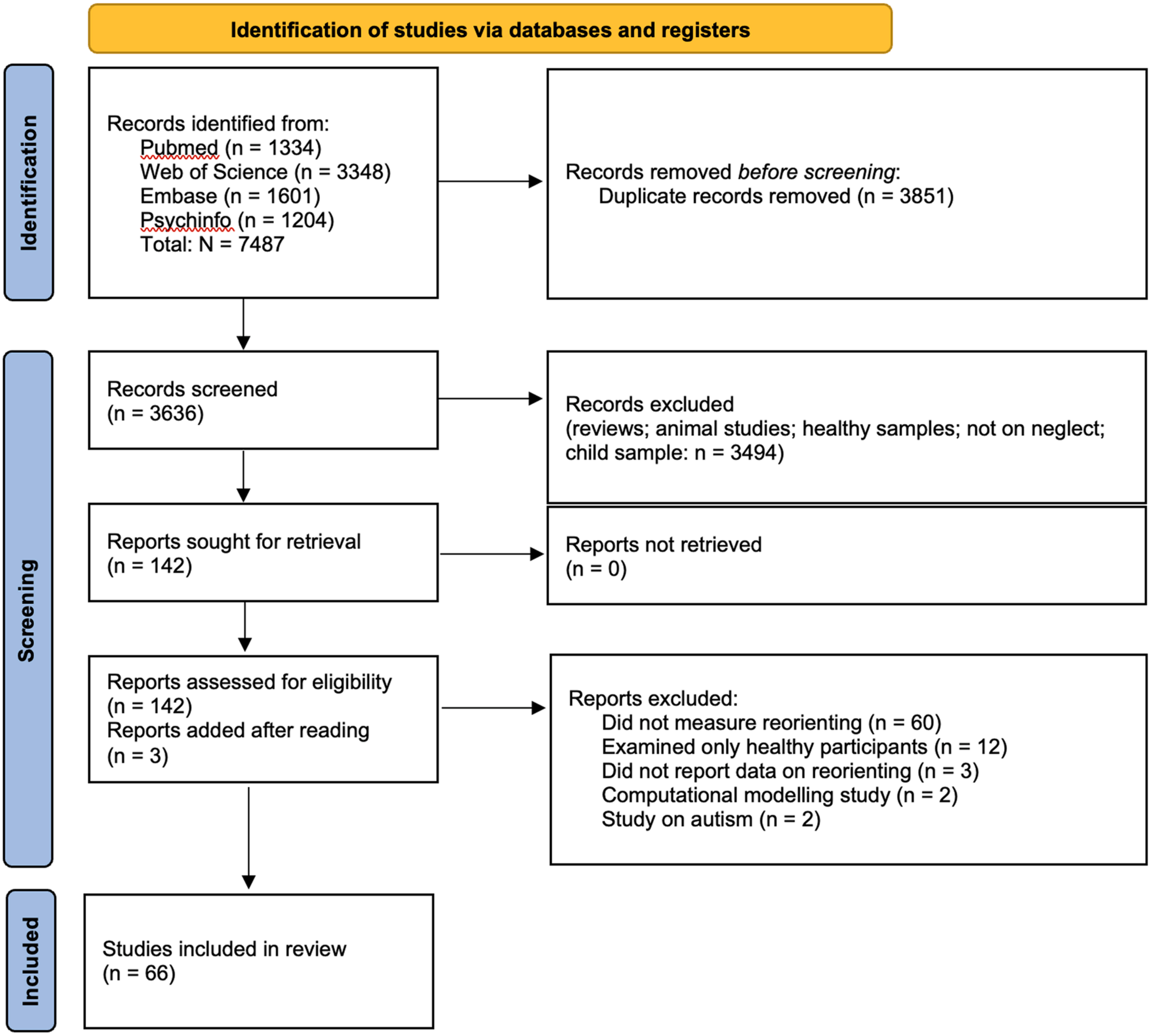

Fig. 1. PRISMA 2020 (Page et al., 2021) flow chart of the literature search and paper selection process.

arising from valid cueing (facilitation), while a negative effect signifies inhibition of return, in accordance with the framework articulated by Posner et al. (1985).

3. Attention capture: Describes the rapid and automatic redirection (engagement) of attention from a neutral starting point toward a peripheral distractor.
4. Disengagement deficit: As outlined by Posner et al. (1984), this term characterizes a specific increase of RTs to, or omission rates of contralesional targets subsequent to spatially invalid cues, in contrast to ipsilesional targets. At the group level, this is conveyed by the statistical interaction between the position of the target and the validity of the cue. In contrast to the validity effect, which may not inherently indicate a difference in hemispace, the disengagement deficit signifies a lateralized (contralesional) disorder.
5. Informativeness of a cue: The degree to which a cue's spatial characteristics (e.g., cue position) or perceptual attributes (e.g., direction of a pointing arrow) are predictively linked to the location of the target.
6. Task-relevant feature: A defining characteristic that participants are asked to react to, and which may be shared by cue and target.
7. Relevance effect: The difference between RTs to targets shown subsequent to a cue sharing task-relevant features (e.g., color), and a cue without this feature.
8. Inhibition of return (IOR): IOR refers to a mechanism that hinders the return of attention to a previously inspected or cued location.

These definitions serve as a foundational framework for our subsequent discussion, enabling a precise and standardized discourse on the identified concepts and findings. Fig. 2 depicts graphical representations of the main effects that may be observed with the spatial cueing paradigm.

4. Insights regarding the orienting of attention following focal brain damage

4.1. Cueing effects provide evidence for exogenous and endogenous attentional mechanisms

Losier and Klein (2001) discriminated between exogenous and endogenous effects by cue position, attributing exogenous effects to the action of peripheral cues and endogenous effects to central (symbolic) cues. Furthermore, they made a clear distinction between pure

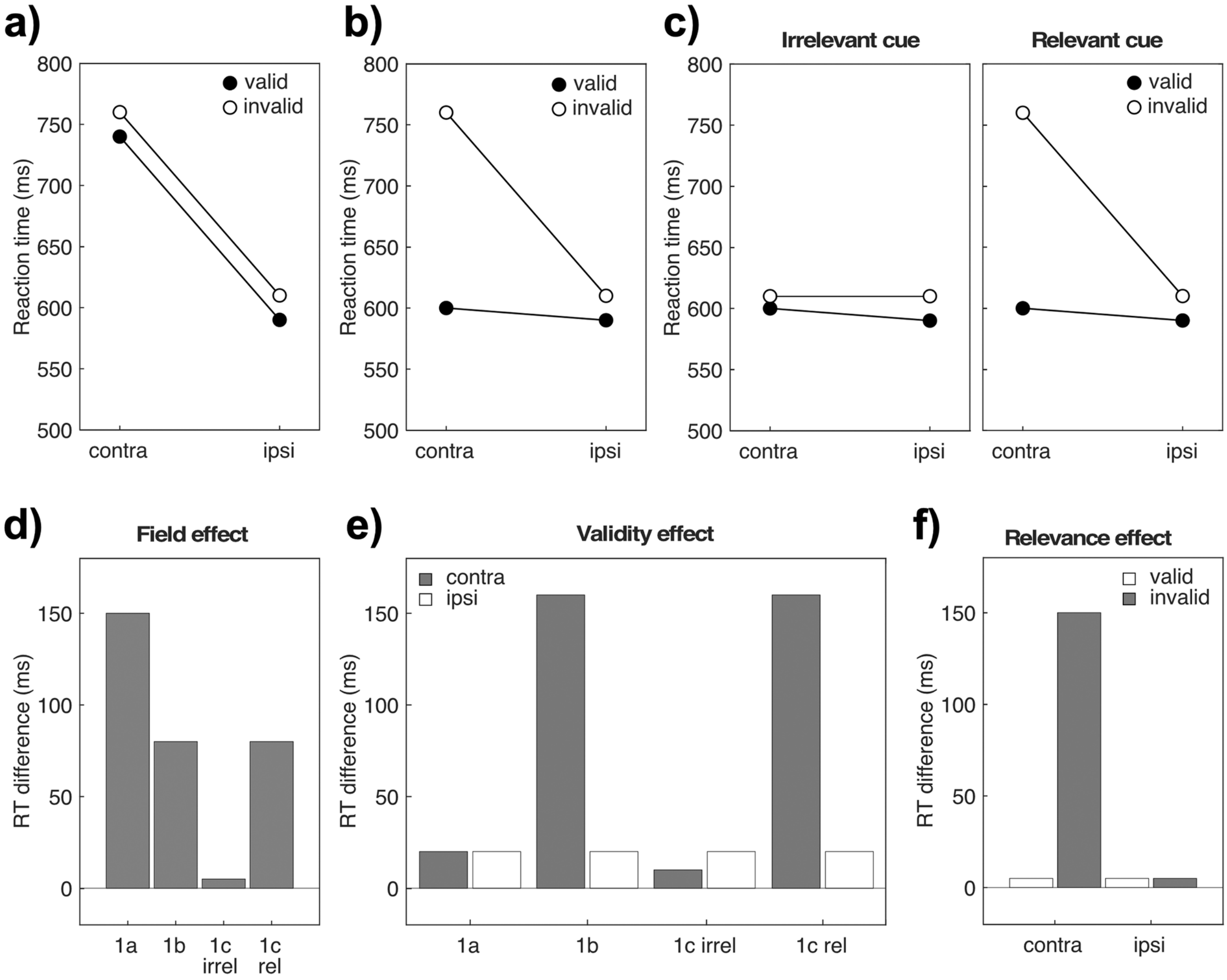

Fig. 2. Hypothetical effects that can be observed with the spatial cueing paradigm. The upper graphs show different scenarios depicting a) a field effect, b) a disengagement deficit (interaction between target position and cue validity), c) a disengagement deficit that is specific for task-relevant cues (interaction between target position, cue validity and cue relevance). The graphs in the lower row depict difference scores for the same hypothetical data, with d) showing the field effect (difference between RTs to contralesional and ipsilesional targets), e) the validity effect (difference between RTs following invalid cues compared to valid cues), and f) the relevance effect (difference between RTs following relevant cues compared to irrelevant cues).

exogenous effects, caused by non-informative peripheral cues, and 'hybrid' effects induced by informative peripheral cues. Nonetheless, this distinction turned out to be inconsequential, as all types of peripheral cues produced a similar disengagement deficit, which was significantly more pronounced than that observed with central cues. Moreover, when focusing solely on central cues, there was no interaction between target position and cue validity, and thus an absence of a significant disengagement deficit. However, this analysis was based on data pooled across different stimulus-onset asynchronies (SOAs) between cue and target. As we will explore further below the duration of the SOA is a significant factor influencing the emergence and extent of the disengagement deficit.

Subsequently, two later studies conducted a systematic examination of attentional orienting in left neglect patients using both peripheral and central cues. These studies encompassed various levels of cue validity and extended SOAs (Bartolomeo et al., 2001; Siéroff et al., 2007).

The experimental paradigm examined the effects of cues with different levels of predictability: informative cues (80% target predictability), non-informative cues (50%), and counter-informative cues (20%) at various SOAs up to 1000 ms. In the non-informative condition, patients exhibited a noteworthy validity effect solely for left targets, particularly noticeable at shorter SOAs (Fig. 3). Conversely, in the 80% validity condition, this effect appeared to endure across all SOAs, extending up to 1000 ms. Nevertheless, within the latter scenario, validity effects also manifested for right targets (excluding the longest SOA), thereby indicating that the disengagement deficit was primarily discernible during briefer SOAs. In the 20% validity condition, which inherently promotes the occurrence of inhibition of return since the target is expected to materialize on the side opposite to the cue, patients displayed a significant validity effect specifically for left targets, but exclusively at the longest SOA. In this condition, their response times were thus faster following invalid cues than valid cues. Consequently, the impact of target predictability appeared to be contingent on the SOA, with validity effects persisting over extended SOAs when predictive cues were employed, while tending to diminish or even vanish during shorter SOAs when cues favored inhibition of return. It should be noted that, even though inhibition of return is observed at long cue-target intervals, it occurs independently of the observer's expectations, supporting the conclusion that it is primarily driven by exogenous processes (Lupianez et al., 2004).

While these studies align with prior findings suggesting a notable bias of exogenous attention that is modulated by relatively preserved endogenous attention (Làdavas et al., 1994a; Morrow and Ratcliff, 1988; Petersen et al., 1989; Posner et al., 1984), it remains challenging to ascertain from behavioral data alone to what extent endogenous cognitive processes are involved (Chica et al., 2014), particularly in patients with neglect. The challenge lies in the difficulty of distinguishing between reduced effects of cue informativeness (indicating partial impairment of endogenous processes) and an increased exogenous bias. One potential approach is to assess the influence of facilitatory and inhibitory cueing effects by comparing them to a neutral control condition, which both studies mentioned above did include. However, it's worth noting that this control condition featured an outlined box positioned at the center of the display, and consequently, *to the right* of the critical contralesional target. As we will see later, some studies support the view that the disengagement deficit of neglect patients is directional (Arguin and Bub, 1993; Posner et al., 1987), and the seemingly 'neutral' cue may have similar effects as a right hemifield cue. This condition therefore can neither be considered as *spatially* neutral (though it was neutral regarding the alerting functions of the cue), nor does it clarify the question whether endogenous processes contribute to the disengagement deficit.

Several studies using relatively pure endogenous conditions (arrow cues with high predictability of the target position) reported a field effect in patients with neglect, but failed to observe significant validity effects and disengagement deficits (Baldassarre et al., 2014, 2016; He et al., 2007; Ramsey et al., 2016; Rengachary et al., 2009). Unfortunately, this result is difficult to interpret since these studies employed exceptionally long SOAs (>3000 ms). Nevertheless, in one study using such long SOAs (Rengachary et al., 2011) a group of 30 patients exhibited a significant disengagement deficit in the acute stage (<15 days after stroke), though not the chronic stage of disease (35 weeks after stroke). The authors capitalized on the observation that the disengagement deficit is evident not just in RTs but also in omission rates. They synthesized both measures into a combined score, thereby tackling a significant methodological challenge encountered in assessing patients with severe spatial attention impairments. Such patients frequently exhibit notably elevated omission rates for contralesional

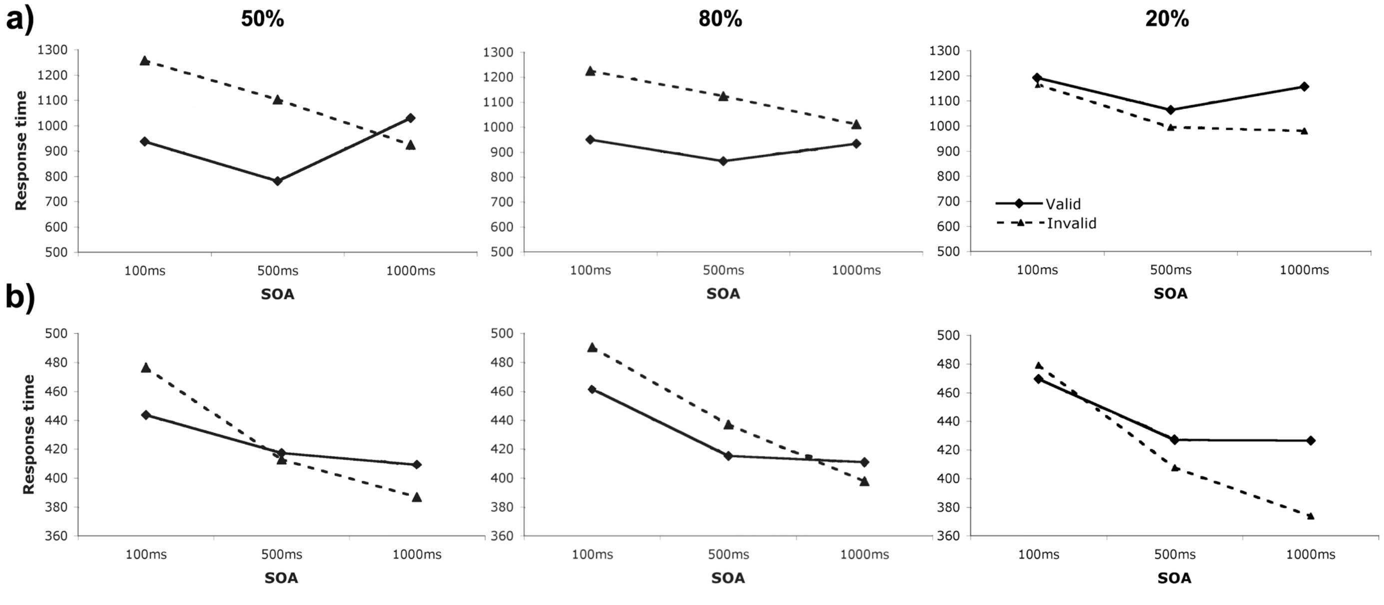

Fig. 3. Effect of SOA and informativeness of the cue on RTs to targets presented in the left hemifield. Subjects were tested with a spatial cueing paradigm that used peripheral cues. Informativeness (indicated in percentage) designates the contingency between cue position and target position (50%: target is as likely to appear at the same position as the cue, as it is likely to appear at the opposite location). a) Patients with left spatial neglect, b) healthy participants. Note the different scales used for both groups (modified from Siéroff et al., 2007).

items, making it impractical to rely solely on RTs when evaluating the disengagement deficit.

Using strongly predictive cues, Osaki et al. (2022) also observed a significant disengagement deficit with arrow cues and SOAs above 3000 ms. Further, a predictive central arrow presented with much shorter SOAs (400 ms) induced a distinctive disengagement deficit, both in patients with isolated intraparietal damage or a lesion to the right temporo-parietal junction (TPJ; Gillebert et al., 2011). In a recent study, Narison et al. (2021) tested ten neglect patients with arrow and gaze cues presented at SOAs of 500 ms, and observed significant benefits of valid cues compared to neutral cues. Unfortunately, their study did not examine effects of invalid cues. Bonato et al. (2009) employed unpredictive central arrows and tested nine neglect patients with SOAs up to 1000 ms. They observed a significant disengagement deficit, but only at the shortest SOA (200 ms). Similarly, Olk et al. (2010) conducted a study involving neglect patients utilizing peripheral, central, and numerical cues in predictive and unpredictive conditions across three different SOAs. They observed significant disengagement deficits with peripheral and central cues, particularly when cues were predictive. The authors noted the intricacy of disentangling exogenous and endogenous processes solely by manipulating SOA, cue type, and predictability. To address this complexity, they introduced an additional experimental condition, where a numerical cue was arbitrarily assigned to a target position (e.g., the number 2 indicating the target's likely appearance in the right hemifield). In this scenario, the cue only attained predictive value for target location through controlled and voluntary processes, bolstered by a high degree of predictability. The outcomes demonstrated a validity effect at extended SOAs and for both hemifields, without any discernible disengagement deficit. These findings support the conclusion that it is primarily exogenous processes that contribute to the disengagement deficit observed in neglect patients.

Finally, a recent study investigated the potential for performance improvement among patients with left neglect through repeated exposure to a spatial cueing task, utilizing both central and peripheral cues (Turgut et al., 2021). In line with a prior study (Làdavas et al., 1994b) patients demonstrated enhanced RTs regardless of cue validity in the peripheral cue condition. However, in the central cue condition, they exhibited reduced validity effects for targets located contralateral to their neglect. These findings indicate that repetitive practice in a spatial attention task may lead to improvements in endogenous mechanisms, while exogenous processes appear to remain relatively stable over time.

Collectively, these findings highlight that the disengagement deficit of neglect patients is most prominent with peripheral cues and at short SOAs (Bartolomeo and Chokron, 2002). This deficit intensifies in situations where cues provide anticipatory information about the target's location and diminishes when the likelihood of the target appearing opposite to the cue significantly exceeds chance levels. These findings align with the conclusions drawn by Losier and Klein (2001), solidifying their significance. Furthermore, there is some suggestion that central, directional cues, such as arrows, may induce a slight but notable disengagement deficit, even when they are unpredictive. Nevertheless, this effect has been documented in only a limited number of studies, typically at short SOAs. In various investigations, the presentation of predictive central cues at extended SOAs failed to elicit a distinctive validity effect, let alone a disengagement deficit. In terms of interpretation, these findings lend support to the notion of an impairment in the rapid, automatic aspects of attention. This interpretation is also supported by studies examining electrophysiological correlates of attention orienting. Lasaponara et al. (2018) observed that patients with spatial neglect showed impaired correlates of the early shift of attention, which is expressed as a lateralized electrophysiological component over the occipito-parietal cortex (see also Lasaponara et al., 2021a). This is coherent with earlier studies suggesting impaired early event-related potentials associated with fast orienting of attention (Deouell et al., 2000; Di Russo et al., 2008). In contrast, the same patients exhibited intact supramodal mechanisms of attentional engagement, which appear in later stages of processing following a cue and are measured at frontal electrode sites.

Additional support for the presence of a deficit in exogenous aspects of attention is derived from studies focusing on the engagement (or capture) of attention. Gainotti et al. (1991) reported on the occurrence of automatic, ipsiversive shifts of the eyes in patients with right brain damage, referred to as 'magnetic gaze attraction'. This phenomenon has since been more formally assessed using eye-tracking technology in neglect patients, persisting even after substantial clinical recovery (Pflugshaupt et al., 2004; Ptak et al., 2009, 2007). Magnetic gaze attraction reflects a pathological engagement of attention toward ipsilesional stimuli (Gainotti et al., 1991; Schnider et al., 2011). Siéroff et al. (2007) quantified engagement using the formula (left valid) – (right valid) and observed a highly positive difference score in neglect patients, indicating a right-sided bias in attentional engagement. A further manifestation of this right-sided bias is the absence or decrease of inhibition of return for right-sided targets in patients with neglect, as observed in (Bartolomeo et al., 1999; Bourgeois et al., 2012). It is thus crucial to note that a comprehensive understanding of the origins of the disengagement deficit requires consideration of potential pathological engagement of attention.

The absence of robust control conditions complicates the determination of whether the disengagement deficit has an independent component, distinct from pathological engagement of attention. Further, it is difficult to disentangle whether it stems from an amplified influence of exogenous processes, a weakening of endogenous processes, or a combination of both. Moreover, the exogenous-endogenous dichotomy is almost exclusively discussed in the context of the three experimental variables SOA, cue position (peripheral vs. central), and cue predictiveness. However, as outlined in Section 4.8, another significant factor influencing performance in cueing tasks is the patient's attentional set, which seems to result from a confluence of automatic and voluntary influences. Furthermore, it is worth noting that the discussion regarding the effects of peripheral and central cues relies on studies that have typically examined only one type of cue. A comprehensive investigation with a sufficiently large patient group, that encompasses both peripheral and central cues, presented at various SOAs and featuring different levels of predictability, is absent from the literature.

4.2. *The time-course of the disengagement deficit*

Much evidence regarding the time-course of the disengagement deficit, as reflected by the influence of SOA between cue and target, has been discussed in the preceding section. Losier and Klein (2001) reported a notable impact of SOA between cue and target on the magnitude of the disengagement deficit following right hemisphere damage. The deficit was most pronounced at the shortest SOAs (50–100 ms) and exhibited a rapid decline with increasing SOAs. In contrast, according to their meta-analysis patients with left hemisphere damage displayed a relatively modest disengagement deficit across all SOAs.

Two systematic studies investigated the influence of SOA and cue validity on the performance of patients with left neglect (Bartolomeo et al., 2001; Siéroff et al., 2007). They observed a dynamic interplay between SOA and cue validity. Specifically, non-informative cues and strongly informative cues (80% validity) produced robust disengagement deficits at both short and long SOAs. In contrast, inhibition of return only became evident when cues were counter-informative (20% validity).

Bartolomeo et al. (2001) interpreted these findings as evidence of an interaction between exogenous and endogenous attention. They suggested that the disengagement deficit primarily stems from exogenous processes but can be modulated by endogenous processes. According to this perspective, endogenous mechanisms, particularly active when informative cues are employed, can prolong the duration of validity effects, especially at longer SOAs. However, they can only reverse validity effects when cues are counter-informative and at longer SOAs. As mentioned in the preceding section, this interpretation overlooks the crucial role of the patient's attentional set, which, though attributed to endogenous processes, is pivotal in the emergence of the disengagement deficit (see Section 4.8).

4.3. Spatial specificity of the disengagement deficit

Early investigations sought to address the question of whether the disengagement deficit is directional (i.e., manifesting only when patients are required to shift attention away from the lesioned hemisphere) or hemifield-specific (i.e., confined to attention shifts within the contralateral hemifield, irrespective of their direction). Posner et al. (1987) supported the former perspective, demonstrating that patients exhibited disengagement deficits within each hemifield when the shift was directed contralaterally. In contrast, Baynes et al. (1986) found that when cue and target were arranged vertically, patients with right hemisphere damage only displayed validity effects in the left hemifield. However, in their single-patient study, Arguin and Bub (1993) were unable to replicate this finding. Instead, they observed no difference between the hemifields for vertical shifts, while a horizontal directional deficit was evident only in the left hemifield. These results lend support to the directional view, although the data remain contentious, and this subject has not been thoroughly explored in more recent research. For instance, one problem is that validity effects appear to be more pronounced when the cue and target appear in opposite hemifields as opposed to within the same hemifield, as noted by Posner et al. (1987). Additionally, the effects become larger as the eccentricity of the cue and target positions increases (Hamilton et al., 2010). Consequently, while a directional deficit appears to best account for the data, it seems to be modulated by the positions of the cue and target in egocentric coordinates.

Another crucial point pertains to the dependency of the disengagement deficit on the existence of a spatial placeholder. Rastelli et al. (2008) observed that the deficit manifested only when the cue was characterized by the onset of a peripheral object (outline box), whereas an offset (disappearance) of the box solely produced a field effect. In a preceding study, D'Erme et al. (1992) had already demonstrated that the contralesional slowing of RTs in patients with neglect is critically contingent on the presence of peripheral boxes. Therefore, the disengagement deficit does not materialize in a space lacking objects but rather in space that is segmented into visual objects.

4.4. Relationship between disengagement deficit and spatial neglect

Early investigations consistently revealed that, regardless of the side of the brain lesion, patients with spatial neglect exhibited substantially larger disengagement deficits compared to patients without neglect (Losier and Klein, 2001; Morrow and Ratcliff, 1988; Petersen et al., 1989). This finding has been corroborated in subsequent research, numerous times (Bartolomeo et al., 2001; Bonato et al., 2009; Chica et al., 2012; Hamilton et al., 2010; Olk et al., 2010; Rastelli et al., 2008; Schurmann et al., 2003; Siéroff et al., 2007).

Nevertheless, a number of reports failed to identify a significant disengagement deficit (Baldassarre et al., 2014, 2016; Ekman et al., 2018; Lasaponara et al., 2018, 2021b), or presented mixed results across patients (Dukewich et al., 2012; Guilbert et al., 2016; Lasaponara et al., 2021a; Sacher et al., 2004; Wansard et al., 2015). It is worth noting that some of these studies primarily reported a field effect, which entails slower response times in the contralesional visual field. This effect is often associated with posterior damage in either hemisphere, and is thus a relatively unspecific finding (Ptak and Pedrazzini, 2021).

It is also important to recognize that studies which failed to observe a disengagement deficit in patients with neglect frequently employed prolonged cue-target intervals or evaluated attention with central cues (Baldassarre et al., 2014, 2016; Ekman et al., 2018; Lasaponara et al., 2021b), both of which are unlikely to yield consistent disengagement deficits. Studies investigating subacute patients using peripheral cues and shorter SOAs almost always revealed significant disengagement deficits among participants with neglect. However, as mentioned earlier, patients with severe spatial deficits may miss many contralesional items, even when the cue-target interval is very long. Considering RTs and omission rates, as done by Lasaponara et al. (2018) or Rengachary et al. (2011) may therefore be a more sensitive approach when identifying a disengagement deficit in patients with neglect.

4.5. Cross-modal cueing effects

Several studies have sought to address whether the disengagement deficit following damage leading to spatial neglect is specific to a given sensory modality. Farah et al. (1989) investigated eight patients with spatial neglect and found evidence of a disengagement deficit for visual targets when preceded by either visual or auditory cues. When directly comparing the magnitude of the disengagement deficit in the two conditions, the authors did not identify a significant difference. However, it's worth noting that this might result from the lack of statistical power, as the effect appeared more pronounced in the visual condition (198 ms) than in the auditory condition (125 ms), though there was also a more rapid decline of the disengagement effect with increasing SOA in the visual condition.

Golay et al. (2005) reported similar results when using static or dynamic auditory cues delivered through headphones. The dynamic cues were perceived as a sound moving from one ear to the other. While the authors observed a disengagement deficit with static cues, it only manifested at shorter cue-target intervals. In contrast, dynamic left-to-right sound cues resulted in a disengagement deficit for left-sided targets, even with longer intervals. Kaufmann et al. (2022) explored the potency of right-to-left auditory cues in improving spatial neglect. They observed better performance in a cancellation test and in eye-movement measures after prolonged (10–15 min) spatial cuing with music. Finally, Shida et al. (2022) examined whether trunk position may impact the magnitude of the disengagement deficit in 18 patients with left neglect. This idea was based on the observation that neglect appears to be contingent on the position of the trunk, which may reflect a proprioceptive or vestibular contribution to an egocentric reference frame (Karnath, 1994). Shida et al. (2022) found that the disengagement deficit was greatest when the patients' trunk was turned to the left of their viewing axis. This finding indicates that, although the disengagement deficit primarily reflects a disorder of spatial attention, its expression also depends on the body-centered reference frame.

These cross-modal cueing effects, however, diverge from the results of Schurmann et al. (2003), who found a significant disengagement deficit in a group of neglect patients only when both the cue and target were visual. When cues were auditory and targets were visual, or when cues were visual and targets were auditory, no effect of cue validity was observed. Guilbert et al. (2016) suggested that cross-modal cueing effects might only be evident when the response requires target localization (e.g., a left-right response) but not in pure detection tasks. Nonetheless, this suggestion does not align with the significant cross-modal cueing effects observed in detection tasks reported by Farah et al. (1989) and Golay et al. (2005).

Variations in the effects of spatial cues could stem from distinct spatiotopic arrangements within sensory systems, with the visual system being more rigorously lateralized and demanding greater precision in localization abilities (Bartolomeo and Chokron, 2001). In addition, according to Schurmann et al. (2003) auditory cues may impact attention less than visual cues because even when presented monaurally, they are processed by both cerebral hemispheres. However, this proposal hinges on the assumption that cueing effects operate through hemispheric activation, rather than spatial facilitation. To address this issue, further research could systematically investigate cross-modal interactions involving other modalities (e.g., tactile, or vibratory) that are known to have purely crossed hemispheric representation.

4.6. Supra-spatial cueing effects

While most studies of cueing effects in brain-injured patients have primarily focused on spatially lateralized attention, a limited number of reports have explored whether cueing effects exclusively pertain to attentional shifts in space or may extend to other cognitive dimensions. For example, Egly et al. (1994) conducted experiments involving patients with damage to either the left or right hemisphere using a modified spatial cueing task. This task incorporated visual boundaries to segregate space into discrete perceptual objects. The objective was to assess attentional shifts both between and within objects, though both conditions necessitated attentional shifts in space as well. The study revealed that patients with right-hemispheric damage exhibited increased validity effects for contralesional positions, though the object-based component was similar for left and right targets. Conversely, patients with left-hemispheric damage displayed increased object-based components for contralesional targets. This implies that damage to the right hemisphere results in a spatial deficit, whereas damage to the left hemisphere leads to an object deficit. However, the latter observation, indicating an object deficit with left-hemispheric damage, was based on very limited number of patients and could not be replicated in a subsequent investigation (List et al., 2011). In another study, Behrmann et al. (1995) devised a cueing task where all stimuli, including cues and targets, were non-lateralized. However, the response effector (i.e., finger) was lateralized. They employed two central targets, each associated with a specific key press using either the index or middle finger. An informative arrow cue indicated the finger most likely to be used in the upcoming trial. The results revealed a notable validity effect for left finger presses, which the authors interpreted as evidence for cueing effects in what they termed 'response space.' Nevertheless, since the validity effect was observed for the finger located further to the left, these findings could still be explained by lateralized facilitation effects without the need to evoke a spatial code in response space. Patients may encounter difficulties when shifting attention toward any item situated more to the left, whether it's a visual target or the responding finger. Thus, distinguishing these findings from the supra-modal attentional deficits discussed in the preceding section is a challenging task.

In another study, Ptak et al. (2002) reported an observation in a single neglect patient, which suggested simultaneous cueing effects in both spatial and color dimensions. In this experiment, the patient was presented with colored shapes to the left and right of fixation, preceded by a cue word indicating the stimulus feature he was expected to identify (i.e., color or shape). While the cue word was centrally displayed and predictive regarding the probed feature, the patient received no advance information about the position of the stimulus to be identified. The results showed enhanced performance for contralateral positions when the patient identified the cued feature, such as color. This finding presents a challenge to a purely 'spatial' explanation, as the cognitive shift induced by the cue operated between two feature dimensions, rather than two positions in space.

A conceptually similar experiment was conducted by Pun et al. (2010), albeit with central cue words referring to different moments in time (i.e., past, present, or future). Patients with left neglect exhibited slower response times for left targets following cues indicating the future compared to cues indicating the past. This suggests that time may be represented along a left-right gradient, and the cognitive shift may function within a higher 'spatio-temporal' representation. A similar spatial arrangement is presumed to underlie the representation of numbers; however, a cueing experiment involving numbers failed to reveal significant cueing effects in patients with neglect (Bonato et al., 2009).

4.7. Training effects in spatial cueing tasks

A limited number of studies have explored the potential for recovery and improvement of spatial attention through training in spatial cueing tasks. In one study by Làdavas et al. (1994b), 12 neglect patients underwent 30 therapy sessions in a cueing task that employed central arrow cues. Over the course of the therapy sessions, patients demonstrated a decrease in error rates for both valid and invalid trials, with slightly more significant improvement observed in the former. Moreover, there were some indications that training in the cueing task had an impact on performance in paper-and-pencil tests assessing spatial neglect. In a subsequent study by Sacher et al. (2004), a good recovery of the disengagement deficit was suggested over time, albeit based on a small number of patients. Butler and Eskes (2014) attempted to ameliorate spatial attention by using passive limb movements but found an improvement in the disengagement deficit in only one of three patients.

Furthermore, Van Vleet et al. (2020) investigated the effects of 12 weeks of tonic and phasic alertness training on spatial attention in 24 patients with neglect. Regrettably, this study solely considered the field effect as an outcome measure and did not provide insights into the disengagement deficit. The authors did report a significant enhancement of the field effect in the intervention group, indicating that training in fundamental non-spatial attention may also have secondary effects on spatially lateralized functions (see Robertson et al., 1998 for a similar finding).

In summary, only a limited number of studies have specifically addressed the recovery of spatial attention as assessed by a spatial cueing task. Furthermore, only one study focused on performance in a spatial cueing task as an outcome measure, with a primary focus on the field effect. It is noteworthy that, except for the study by Van Vleet et al. (2020) employing alertness training, other neglect intervention techniques such as visual scanning, optokinetic stimulation, and prism adaptation have not been systematically evaluated using a spatial cueing paradigm.

4.8. Modulation of spatial attention by task-relevance and reward

As discussed in Section 4.1, both peripheral and central cues engage varying degrees of endogenous and exogenous attentional processes. In an investigation by D'Erme et al. (1992), the anticipated contralateral validity effect was observed in neglect patients when a lateralized white dot served as a cue. However, when two white boxes were presented 167 ms prior to the target, they observed a similar validity effect, despite the boxes being displayed in each hemifield. This finding suggested that patients initially oriented their attention towards the right box, indicating attentional capture even in cases of equal visual stimulation in both the left and right hemifields. Notably, this study stands as one of the rare early instances where different characteristics of cues were examined in terms of their impact on the validity effect.

It is not surprising that physically salient cues are more effective in capturing attention compared to less conspicuous cues. For instance, an abrupt visual onset strongly elicits reflexive attention towards the area where the stimulus appears, as highlighted by Jonides and Yantis (1988) and Yantis and Jonides (1984). However, the question of whether this effect is solely driven by automatic mechanisms or can be influenced by goal-oriented processes remains a topic of ongoing debate, as discussed by several authors (Folk and Remington, 2006; Folk et al., 1992), (Theeuwes, 2004, 2010; Yantis and Egeth, 1999). In the context of assessing the influence of goal-related and motivational factors on spatial attention in patients with neglect, insights from the extinction paradigm suggest that the detection of the contralateral stimulus is affected by its similarity to the ipsilesional distractor on the relevant dimension (as indicated by studies conducted by Gilchrist et al., 1996; Ward et al., 1994). However, a study conducted by Snow and Mattingley (2006) using a flanker paradigm presented contrasting results. In this study, participants were tasked with identifying either the shape or the color of a central letter while concurrently disregarding the left and right flanker letters. One of the two flankers shared a feature with the central target, either the feature that needed to be identified (the relevant feature) or the other, irrelevant feature.

Healthy control participants demonstrated a significant flanker effect solely with respect to the task-relevant dimension. This meant that they exhibited slower identification of the central feature (e.g., color) when a flanker shared the same shape but had a different color. In contrast, while showing a similar pattern with task-relevant flankers, neglect patients' performance was also impacted by ipsilateral flankers that differed from the target in the task-irrelevant dimension (e.g., having a different shape when patients were focusing on color). The authors concluded that the impairment of spatial attention in neglect results in an increased prioritization of any stimulus feature on the ipsilateral side, whether it is relevant or irrelevant to the task. However, this finding contrasts with several studies reporting a substantially heightened attentional capture by ipsilateral distractors only when they shared a relevant feature with the target, with entirely irrelevant distractors having no effect.

In one study, participants reacted to a peripheral target defined by its color (a red circle), presented alongside a distractor (a green square) in the opposite hemifield (Ptak and Schnider, 2006). The target display was preceded by a peripheral cue, which was either identical to the target (and thus task-relevant) or identical to the distractor (task-irrelevant). Participants were instructed to respond to the target while disregarding the cue. In contrast to the findings of Snow and Mattingley (2006), neglect patients demonstrated a significant disengagement deficit solely when task-relevant cues were used, with task-irrelevant cues having no impact on their performance. One possible explanation for this difference lies in the distinct temporal dynamics of the cueing task and the flanker task. In the former, there was an interval of 300 ms between the cue and the target, while in the latter, flankers and the central target were presented simultaneously. Indeed, at very short intervals between the cue and the target (100 ms), relevant and irrelevant cues captured attention to a similar extent, and a significant effect of cue relevance only emerged at longer intervals (Ptak and Golay, 2006). Thus, regardless of their task-related characteristics, all ipsilesional cues captured the attention of patients with neglect at very short delays. The impact of task-irrelevant and task-relevant cues appears to diverge at 300 ms, with the former ceasing to capture attention while the latter continued to bind attentional resources for several hundred milliseconds.

One question arising from these findings pertains to whether the relevance of a cue is automatically associated with a perceptual characteristic of the target or is a feature- and modality-independent quality. For example, when the target is defined by color, relevance could capture attention because of the perceptual similarity between cue and target on the critical dimension. Alternatively, relevance could be entirely dissociated from the concrete perceptual relationship between cue and target. To explore this possibility, neglect patients were asked to respond to one of two targets, either a red circle or the word RED (Ptak and Schnider, 2006). Consequently, the cue was either perceptually similar (in both cases, either a red circle or the word RED) or dissimilar (a red circle when the target was the word RED, or vice versa). The results demonstrated that relevant cues captured attention to a similar extent, whether they were perceptually similar or dissimilar to the target. Thus, task-relevance is not confined to a specific feature shared between the cue and the target but is a feature-independent quality that can be attributed to any characteristic defining the target, as supported by studies employing diverse stimuli such as colored shapes, letters, or words (Pedrazzini and Ptak, 2019; Ptak and Golay, 2006; Ptak and Schnider, 2006, 2010). In a recent meta-analysis, Brown (2022) summarized these findings by concluding that motivationally salient stimuli have an advantage in being detected more easily than neutral stimuli due to their enhanced priority (see also Bourgeois et al., 2016 for a discussion of the effects of motivational salience on selective attention).

Although it may be tempting to liken these motivational effects to endogenous attention, it is important to acknowledge that while they rely on task instructions, their impact is not under voluntary control. Task-related expectancies, typically considered as elements of endogenous processes, may operate beyond conscious awareness (Bartolomeo et al., 2001; Decaix et al., 2002). Thus, motivationally significant stimuli may be granted heightened priority even when participants are unaware of or unable to control their current attentional set.

Extensive behavioral, neurophysiological, and neuroimaging evidence underscores the relationship between attentional selection and action planning, both functionally and in terms of shared neural structures (Doganci et al., 2023; Ptak et al., 2021; Gottlieb, 2007; Grèzes and Decety, 2002; Humphreys and Riddoch, 2001; Mahon et al., 2007; Rowe et al., 2010; Tipper et al., 1992). Task-relevance appears to bias attentional selection by heightening the priority of certain stimuli or stimulus features. Such effects lend support to the notion that the primary biological purpose of attentional selection is to focus cognitive resources on potential action targets (Cisek, 2019; Tipper et al., 1992). Given that actions can lead to either positive or negative outcomes, it raises the question of whether the subjective value of a spatial cue impacts its ability to capture attentional resources. Experiments with healthy participants have shown that the presence of a distractor associated with a monetary reward significantly delays attentional search for a visual target, even if the distractor is inconspicuous and task-irrelevant (Anderson et al., 2011).

Building on this observation, we investigated the effect of task relevance and positive or negative rewards on the contralesional validity effect in a group of neglect patients (Bourgeois et al., 2022). Peripheral cues were either congruent with the target-defining color, rendering them task-relevant, or had a different color from the target, making them task-irrelevant. All task-irrelevant cues were paired with a reward, which was either positive (winning 100), negative (losing 100), or neutral (neither winning nor losing points). Participants were informed that they could win or lose points based on the speed or precision of their response. Unbeknownst to them, the reward was linked to the color of the cue, not their actions.

As expected from previous studies, the task-relevant cue strongly captured attention, significantly increasing the validity effect. Interestingly, among the task-irrelevant cues, only ipsilateral cues associated with negative rewards similarly affected the validity effect. This finding suggests a possible link between spatial orienting and neural systems involved in the evaluation of the biological relevance of external stimuli.

4.9. Anatomical and functional correlates of the disengagement deficit

Losier and Klein (2001) reported that the disengagement deficit induced by peripheral cues was significant for patients with right and left parietal lesions. However, when both groups were included in one analysis, the deficit appeared significantly larger in patient with right hemisphere damage. Some subsequent studies including patients with left and right hemispheric lesions did not perform distinct analyses, or even pooled patients into one large group (Baldassarre et al., 2014; Ramsey et al., 2016). In studies directly comparing the effects of left and right hemisphere lesions, no significant differences were observed (List et al., 2011; Marangolo et al., 1998). However, it's important to note that these investigations did not employ one of the standard paradigms, such as a task involving peripheral or central cues. Instead, they focused on within-object effects or color priming. In contrast, a recent study shed light on the impact of hemisphere involvement. In this study, 71 patients with right-hemisphere damage exhibited a significant contralesional disengagement deficit, while a smaller group of left-hemispheric patients displayed only a cue-independent contralesional field effect or, in some conditions (at extended SOAs), even showed signs of inhibition of return (Ptak and Pedrazzini, 2021). These findings align with earlier research that indicated a notably more pronounced disengagement deficit following right hemisphere damage, suggesting a potential hemisphere-specific relationship (Morrow and Ratcliff, 1988; Posner et al., 1984).

It is worth noting that anatomical findings link the incidence of spatial neglect after left hemisphere damage to the involvement of the superior temporal and inferior parietal cortex (Suchan and Karnath, 2011), and a recent DTI study implied the superior longitudinal fasciculus (Toba et al., 2022). This pattern is analogous to the occurrence of right hemisphere neglect (Golay et al., 2008; Karnath et al., 2004; Mort et al., 2003; Pedrazzini and Ptak, 2020). However, previous studies involving left hemisphere patients in the spatial cueing paradigm primarily relied on identifying patients based on the presence of damage, rather than specifically targeting individuals with spatial neglect. Consequently, a systematic investigation of disengagement deficits in patients with left hemisphere damage, especially those with neglect, has not been conducted to date. We can therefore not draw detailed conclusions about the impacts of exogenous/endogenous orienting, the temporal attributes of spatial attention, or the extent of the disengagement deficit in this specific group of patients with left hemisphere damage.

The findings discussed so far strongly indicate that the disengagement deficit is closely associated with spatial neglect following focal damage to the right cerebral hemisphere. In their seminal report Posner et al. (1984) argued that this deficit is causally linked to damage in the parietal lobes. In their meta-analysis, Losier and Klein (2001) addressed this issue by categorizing patients into two groups: one with damage confined to the parietal lobe and another with damage that could extend into the parietal lobe but was not restricted to it. A direct comparison between these two groups did not reveal any difference regarding the disengagement deficit. Since both groups shared the common characteristic of damage involving the parietal lobe, this finding might suggest that the latter is crucial for the emergence of a disengagement deficit. However, this conclusion is problematic, as the comparison on which it is based did not include a control group without parietal damage and did not account for possible confounding factors such as differences in lesion volume. Therefore, it is impossible to determine the specificity of parietal damage as a predictor of the disengagement deficit based on this comparison. Another crucial point to note is that, while behavioral methods have remained relatively stable over the past 20 years, significant advancements have occurred in the diagnostic precision of neuroimaging techniques and the methodologies for lesion-symptom mapping (Bates et al., 2003; DeMarco and Turkeltaub, 2018; Rorden et al., 2007; Sperber and Karnath, 2018).

It is worth noting that in early studies, the critical damage leading to spatial neglect was often assumed *a priori* to involve the parietal lobe, even though many of these studies did not provide neuroimaging results for their patients. In fact, some reports even used the term 'parietal neglect' to describe the condition (Driver and Mattingley, 1998). Later investigations utilizing techniques like voxel-based lesion-symptom mapping identified the crucial brain lesions associated with neglect in the inferior parietal and superior temporal cortex (Golay et al., 2008; Karnath et al., 2001, 2004; Mort et al., 2003; Pedrazzini and Ptak, 2020). However, following a seminal study by Doricchi and Tomaiuolo (2003) several diffusion tensor imaging (DTI) studies have underscored the significance of frontoparietal disconnections as substantial contributing factors (Bartolomeo et al., 2012; Shinoura et al., 2009; Thiebaut de Schotten et al., 2014, 2005; Urbanski et al., 2011).

While these investigations generally defined spatial neglect as a syndrome characterizing a specific group of patients, other studies have emphasized differences in lesion location between subclasses of neglect, such as space-centered vs. object-centered neglect (Chechlacz et al., 2010; Medina et al., 2009; Pedrazzini et al., 2017), allocentric vs. egocentric neglect (Moore et al., 2023) or extrapersonal vs. personal neglect (Baas et al., 2011; Committeri et al., 2007). Collectively, these studies indicate that neglect arises from disruptions in frontoparietal networks encompassing the TPJ, superior temporal and lateral frontal cortex (Corbetta and Shulman, 2011; Karnath and Rorden, 2012; Molenberghs et al., 2012; Moore et al., 2023). Given the potential dissociations between neglect subtypes, it is important not to unquestionably accept the findings of early studies but rather to explore anatomical markers of the disengagement deficit using modern analysis methods.

A recent extensive lesion study employed contemporary lesion-symptom mapping techniques to investigate voxel-wise predictors of performance in a spatial orienting task (Carter et al., 2017). The study involved seventy patients who did not exhibit visual field impairment and were tested at the subchronic stage using a central cueing (arrow) paradigm. The authors specifically focused their analysis on the field effect, which serves as a global measure of contralesional slowing, and the validity effect. The validity effect was computed as the bilateral difference between the invalid and valid conditions, making it a measure of bilateral orienting of attention. The study revealed that the field effect was linked to damage in the frontal and parietal white matter, whereas the validity effect was more specifically associated with damage to the white matter underlying the superior and inferior parietal lobule. In a different study, Rengachary et al. (2011) examined whether validity and disengagement effects differed between two lesion groups. One group had anterior lesions centered on the ventral frontal cortex and insula, while the other had posterior lesions centered on the TPJ. They observed an increased validity effect in the anterior group, regardless of the hemifield, but found no differences between the groups in terms of the disengagement deficit. Finally, a recent study by Lasaponara et al. (2018) reported a link between damage to frontoparietal fiber tracts and the disengagement deficit, as expressed by the proportion of missed contralesional targets in the critical invalid condition.

However, it is important to note that these findings pertain to strongly endogenous mechanisms of attention orienting. This is because both studies used a central, symbolic cue, and the SOAs between the cue and peripheral target were particularly long, exceeding 3300 ms. As we have discussed in Sections 4.1 and 4.2, conditions with such long intervals are unlikely to reveal a disengagement deficit (Olk et al., 2010). Therefore, these newer studies do not contribute to our understanding of the anatomical underpinnings of the disengagement deficit.

One of the early anatomical studies that shed light on the disengagement deficit compared the effects of superior and inferior parietal damage on spatial orienting task performance (Friedrich et al., 1998). The authors discovered that damage to the TPJ and superior temporal lobe led to more pronounced disengagement deficits compared to damage to the superior parietal lobe (SPL). Moreover, while the SPL group also showed significant validity effects, these effects tended to be similar for both ipsilateral and contralateral stimuli. This suggested that the TPJ is the critical region responsible for lateralized deficits of attention.

Subsequent findings by Molenberghs et al. (2008) affirmed that the involvement of the right inferior parietal lobe results in a lateralized deficit in shifting attention, especially when contralateral stimuli are presented simultaneously with an ipsilateral distractor. More recently, Gillebert et al. (2011) identified a bilateral deficit in a single patient with selective right intraparietal injury. In contrast, a group of patients with damage to the right TPJ only displayed an exaggerated validity effect for contralateral targets, which supported the findings of Friedrich et al. (1998).

Several recent studies have examined attention orienting using a task that measured RTs to colored targets (e.g., blue) preceded by same-colored cues or differently colored cues. As discussed in Section 4.6, cues sharing target-defining characteristics (such as color) are considered task-relevant and strongly capture the attention of patients with neglect when presented ipsilaterally. Ptak and Schnider (2010) reported that the effect of task-relevance was absent or reduced when patients had damage involving the superior premotor cortex, centered on the frontal eye fields. However, this finding was based on a relatively small group of neglect patients. In a subsequent study, Pedrazzini and Ptak (2019) assessed three patient groups with damage to the TPJ, the lateral prefrontal/insular cortex, or subcortical white matter centered on the internal capsule. All three groups exhibited slowed RTs to contralesional targets (field effect), but only the TPJ group displayed a significant disengagement deficit.

In a second study employing the same paradigm, a much larger group of right-hemisphere patients (N = 71) and a smaller group of left-hemisphere lesion patients (N = 12) were tested (Ptak and Pedrazzini, 2021). Lesion-symptom analyses were conducted on the right-hemisphere group using a machine-learning algorithm that considered statistical dependencies between adjoining voxels while simultaneously correcting for lesion volume effects. The disengagement deficit was observed only when cues were task-relevant, and this deficit was associated with damage to the right TPJ, overlapping the dorsal occipital cortex, the angular gyrus, and the posterior superior temporal gyrus (Fig. 4). This finding was further confirmed when analyzing the behavioral results of subgroups of patients, differentiated based on the presence of damage to the TPJ, the right insula, or lesions encompassing both brain regions. The paradigm used in this study slightly differed from the standard Posner task, in that they required go-nogo decisions. This adds a slight, supplementary difficulty compared to the classic task, as participants must inhibit responses to the cues. However, this inhibitory component is unlikely to affect performance significantly, as it predicts slower RTs on go-trials subsequent to task-relevant cues in the valid condition, which was not observed in the studies using this paradigm (Pedrazzini and Ptak, 2019; Ptak and Pedrazzini, 2021; Ptak and Schnider, 2010). Further, the initial study showing disengagement effects with task-relevant cues used a go-nogo paradigm (Ptak and Schnider, 2006). In addition, the modified task consistently identified disengagement deficits in neglect patients with task-relevant cues, and at very short cue-target intervals also with task-irrelevant cues (Ptak and Golay, 2006).

In conclusion, compelling evidence from lesion mapping indicates that the disengagement deficit highlights a crucial contribution of the right TPJ, with some weaker evidence suggesting a contribution from the dorsal premotor cortex, including the frontal eye fields. Notably, none of the studies mentioned above could identify anatomical predictors of attentional capture by task-irrelevant cues, underscoring the significance of considering task relevance in studies of spatial attention

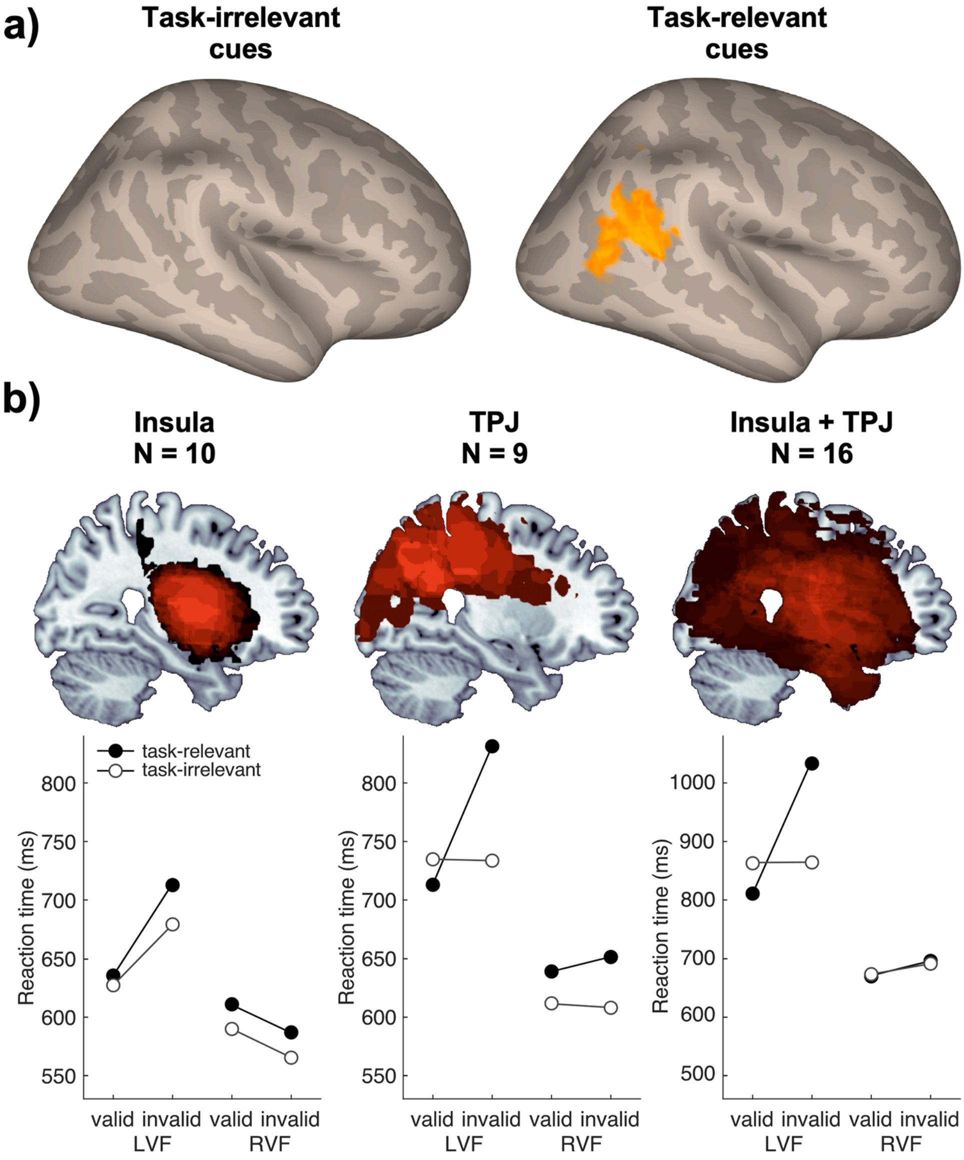

Fig. 4. Anatomical correlates of the effects of task-relevance on the disengagement deficit in patients with right-hemispheric lesions. a) Voxel-based lesion-symptom correlates of the disengagement deficit with task-irrelevant cues (left: no significant voxels identified) and task-relevant cues (right: voxels that reached voxel-level and cluster-level significance). b) Results of three lesion groups in the spatial cueing task with task-relevant and task-irrelevant cues (based on data from Ptak and Pedrazzini, 2021; LVF/RVF: left/right hemifield).

deficits in neglect.

Despite significant methodological advancements and the valuable insights, it offers into the causal roles of specific brain regions in various functions, lesion mapping faces challenges when attempting to identify functional interactions between different brain areas. This issue is particularly salient since numerous studies with limited patient numbers have been published, failing to pinpoint a common brain area responsible for spatial attention disorders like spatial neglect (Molenberghs et al., 2012).

Another concern arises from the fact that focal brain lesions may have widespread effects that extend well beyond the damaged area, potentially impacting the preserved hemisphere (Alstott et al., 2009; Buckner et al., 2009; Gratton et al., 2012). In their study of functional activations in eleven neglect patients performing a spatial cueing task during functional imaging, Corbetta et al. (2005) observed that the field effect correlated with increased activity in left hemisphere regions, particularly in the superior parietal cortex and visual cortex, and decreased activity in the corresponding regions of the injured right hemisphere. They also reported that the activity of the right superior temporal gyrus and precuneus predicted the presence of a validity effect and its improvement in chronic neglect. However, the absence of a significant disengagement deficit in their patients is likely because they utilized a central arrow cue and employed exceedingly long cue-target intervals. Additionally, their study did not involve brain-injured patients without neglect, leaving uncertainty about whether the findings are specific to neglect or represent a non-specific effect of right-hemisphere damage. Indeed, Umarova et al. (2011) and (Umarova et al., 2016) found that a relative imbalance between left parietal and right parietal activation was present regardless of the presence of spatial neglect. The relative 'hyperactivation' of the left parietal cortex appears to reflect an acute state of the brain following unilateral stroke to a single hemisphere. Furthermore, the study indicated that the field effect was primarily correlated with activations across left dorsal frontoparietal regions, which the authors interpreted as a compensatory mechanism for the lateralized bias of attention.

Regrettably, these studies remain limited in number, as they tackle important challenges associated with engaging neglect patients in active fMRI tasks. Indeed, researchers must deal with issues like excessive movement, leading to acquisition artifacts, or patients showing difficulties with following instructions. A more convenient alternative is to investigate resting-state functional connectivity (rs-FC), which merely requires patients to remain still without engaging in a cognitive task. Multiple studies examining functional connectivity (FC) have revealed that one of the primary outcomes of stroke is a significant reduction in functional interactions between the two hemispheres, affecting both homotopic and heterotopic regions (Baldassarre et al., 2014; Carter et al., 2010; Ptak et al., 2020). In their examination of task-based FC, He et al. (2007) focused on the same 11 patients who had been scanned previously while performing the spatial cueing task developed by Corbetta et al. (2005). They noted that an imbalance of FC between the right and left intra-parietal cortex (IPC) and between the supramarginal gyri (SMG) predicted the disengagement deficit in the acute phase following a stroke. A subsequent study by the same group (Baldassarre et al., 2014) found that a principal component score indicative of neglect was linked to a decreased interhemispheric rs-FC between the right dorsal frontoparietal cortex and widespread regions of the left hemisphere. Furthermore, Ramsey et al. (2016) also observed that the decrease in interhemispheric rs-FC, particularly across the dorsal frontoparietal cortices, predicted spatial attention deficits. However, these later studies did not specifically concentrate on results obtained using the spatial cueing task; instead, they computed compound scores of spatial neglect based on several tests. As a result, these findings do not directly inform us about the functional predictors of the disengagement deficit.

A recent study focused on identifying rs-FC predictors associated with the disengagement deficit for task-relevant and task-irrelevant cues based on target color (Ptak and Pedrazzini, 2021). The study included twenty-six patients with right-hemisphere damage who, on average, exhibited a significantly higher level of attentional capture when cues were task-relevant compared to when they were task-irrelevant. The rs-FC analyses did not reveal any predictors for the field effect or the validity effect. Instead, they identified three predictors for the relevance effect (i.e., the difference between the validity effects of task-relevant cues compared to task-irrelevant cues). These predictors included the connection between the right insula and the right TPJ, the right amygdala and the right IPC, and the right dorsolateral prefrontal cortex (dPFC) with neighboring regions, including the middle frontal gyrus (Fig. 5). Notably, healthy controls exhibited very similar rs-FC patterns in these regions, with one exception: the right dPFC showed both local connectivity and remote connections to the insula and the TPJ.

In summary, the key finding of this study suggests that the primary predictor of the disengagement deficit with task-relevant cues is the absence of long-range effects of the dPFC on the insula and the TPJ, while the latter regions still maintain connectivity with each other. It is noteworthy that the level of functional connectivity is closely linked to the existence of structural connections (Hermundstad et al., 2013). Consequently, compromised functional connectivity between the dPFC and the TPJ indicates structural deficits within the superior longitudinal fasciculus (SLF), recognized as a significant fiber tract associated with spatial neglect (Thiebaut de Schotten et al., 2014, 2005). These findings underscore the importance of structural and functional interactions involving several brain regions as the anatomical correlate of the disengagement deficit, a topic that will be discussed in the following section.

5. Disengaging attention with spatial neglect: an update

5.1. Summary of the main findings regarding the disengagement deficit

The present literature review yields several key conclusions, expanding upon earlier findings as proposed by Losier and Klein (2001). These conclusions will be succinctly summarized before we introduce an anatomical and functional model of attentional disengagement, rooted in lesion studies involving patients with spatial neglect:

a) The disengagement deficit is undeniably linked to spatial neglect and serves as a hallmark feature of this condition.
b) Unilateral right-brain damage leading to neglect predominantly skews attention toward distracting ipsilateral information. Ipsilateral cues impose an attentional cost, whereas there is limited evidence supporting the notion that contralateral cues confer attentional benefits.
c) The disengagement deficit is markedly more pronounced when prompted by peripheral (spatial) cues in comparison to central (symbolic) cues.
d) The severity of the disengagement deficit is most pronounced when the cue-to-target interval is short (measured as SOAs).
e) The disengagement deficit peaks when cues hold predictive value regarding target location. Cue predictiveness extends the temporal window during which the disengagement deficit can be observed.
f) The presence of a disengagement deficit is contingent upon the task relevance and reward value of a spatial cue.
g) Auditory cues may potentially induce a disengagement deficit when located in the periphery, albeit this effect tends to be less pronounced compared to visual cues.
h) Patients with neglect may exhibit challenges in shifting attention within cognitive dimensions beyond space, including those related to object features or motor representations.

Drawing from the extensive literature reviewed, we can assert the strength of evidence for points a-f, while points g and h necessitate further validation. These findings can be related to theoretical models within the domain of attentional selection, marking a transition from

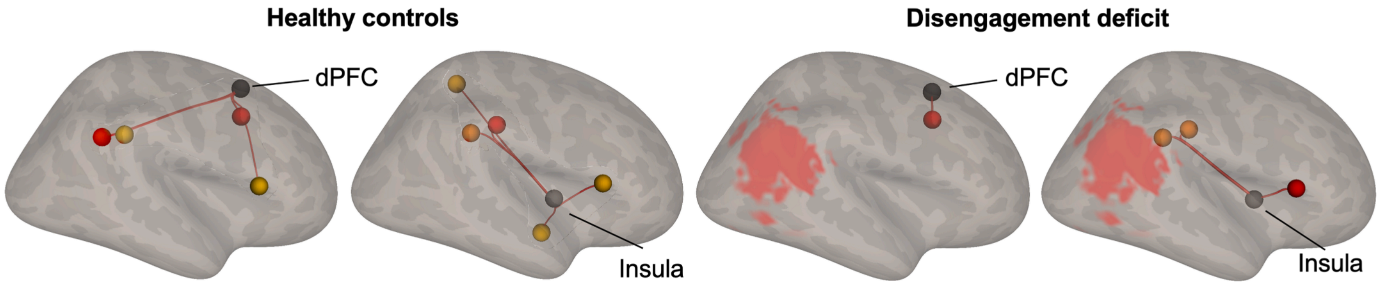

Fig. 5. Functional connectivity between the dorsal prefrontal cortex (dPFC) and the insula in healthy participants (left) and patients with a disengagement deficit following damage to the right temporo-parietal junction (TPJ, right).

early purely spatial paradigms to more inclusive ones incorporating higher-level (non-spatial) attributes.

Early theories posited that attention functioned as a spatial spotlight (Posner, 1980), internalized gaze (Rizzolatti et al., 1987), or zoom-lens (Eriksen and St. James, 1986), primarily focusing on mechanisms associated with spatial selection, attentional dynamics, and overt eye movements. However, these mechanistic analogies struggled to predict object-based selection and multi-dimensional selection effects (Cave and Bichot, 1999). An alternate viewpoint suggests that spatial cues modulate attention by reducing uncertainty. According to this perspective, cues aid in resolving uncertainties related to target locations by mitigating random noise within a spatial selection system (Pashler, 1998). The importance of predictions is exemplified by the finding that patients with neglect generate predictions about sensory events based on statistical regularities characterizing right-sided events only, suggesting that a deficit in predictive coding contributes to the spatial attention deficit (Doricchi et al., 2021). This perspective aligns better with the multi-dimensional attention shifting effects described in Section 4.6, as the reduction of uncertainty can theoretically act on any stimulus feature (e.g., color, shape, or multi-dimensional response mapping).

Another vital postulation in understanding findings with neglect patients distinguishes between exogenous and endogenous attention. The recognition that two temporally distinct attentional mechanisms contribute to spatial cueing effects is widely embraced (Bartolomeo and Chokron, 2002; Carrasco, 2011; Müller and Rabbitt, 1989). This distinction aids in explaining differences between peripheral and central cues, the influence of cue predictiveness, and the temporal dynamics of cueing effects. Nonetheless, as discussed in Section 4.6, several studies propose that cue-related effects may operate at higher representational levels, which poses challenges for a strict exogenous-endogenous distinction primarily related to the automaticity and temporal dynamics of attention. This dichotomy has also sometimes been conflated with or considered equivalent to other categorizations, such as bottom-up vs. top-down, reflexive vs. voluntary, or stimulus-driven vs. goal-directed attention (Corbetta and Shulman, 2002; Hopfinger and Ries, 2005; Làdavas et al., 1994a; Yantis and Jonides, 1990). Criticism has been directed at these dichotomies for their inability to adequately account for factors influencing attentional selection, particularly the role of item history or cue relevance (Awh et al., 2012).

Saliency-based theories focus on physical characteristics that make a stimulus stand out in its surroundings, thus favoring attentional selection (Egeth and Yantis, 1997; Fecteau and Munoz, 2006; Itti et al., 1998; Parkhurst et al., 2002; Yantis and Jonides, 1984). An abrupt onset is one well-studied saliency factor, known to trigger an automatic shift of covert or overt attention towards the newly appeared stimulus (Theeuwes et al., 1999; Yantis and Jonides, 1984, 1990). However, the concept of saliency falls short in explaining attentional biases associated with goal-oriented processes, motivational factors (e.g., associated rewards), and statistical properties of environmental objects (e.g., likelihood of occurrence). Recent theories, therefore, prefer the term "priority" to describe a comprehensive neural property encompassing inputs at both the stimulus and subject levels (Bisley and Goldberg, 2010; Gottlieb, 2002; Yantis and Johnson, 1990). Priority is often conceptualized as a high-level computational property of environmental objects or features, represented within a spatiotopic map (Chelazzi et al., 2014; Gottlieb, 2012; Ptak and Fellrath, 2013; Sprague et al., 2018). Hence, theories of attentional selection have evolved from relatively mechanistic and space-centered accounts towards more comprehensive models, considering a multitude of factors influencing attentional selection (Ptak, 2012; Anderson and Kim, 2019; Awh et al., 2012; Gottlieb, 2012; Scolari et al., 2015; Yantis and Serences, 2003). Importantly, these different accounts are not mutually exclusive but rather integrate evolving knowledge to provide a theoretical framework for the anatomical model of the disengagement deficit discussed in the next section.

5.2. An interactive anatomical model of attentional capture and disengagement

The anatomical findings discussed in Section 4.9 provide insights into the mechanisms underlying attention capture and disengagement, highlighting the intricate interplay among various right-hemispheric brain regions (Fig. 6). At the core of this model is a functional right-hemispheric triangle comprising the TPJ, a dorsal frontal unit composed of the dPMC and the dPFC, as well as the insula. These regions further interact with the IPC, which serves a general role in both spatial and non-spatial attentional selection.

The right TPJ, while characterized by somewhat vague anatomy, is situated at the posterior end of the lateral sulcus and encompasses the angular gyrus, parts of the supramarginal gyrus, and the posterior superior temporal gyrus (Carter and Huettel, 2013; Igelstrom and Graziano, 2017; Mort et al., 2003). It has been described as a functional hub receiving convergent inputs, enabling it to support a range of high-level cognitive processes (Buckner et al., 2009; Carter and Huettel, 2013). This characterization primarily stems from functional neuroimaging studies that have shown TPJ activation during tasks related to diverse cognitive functions, such as memory, social cognition, and attention (Cabeza et al., 2012; Corbetta et al., 2008; Corbetta and Shulman, 2002; Decety and Lamm, 2007; Saxe and Kanwisher, 2003). However, while its role in memory and social cognition is primarily supported by neuroimaging findings, its involvement in attention has found more robust backing from both functional neuroimaging and lesion studies.

Faced with an apparent ubiquity of right TPJ activations to various tasks, diverse authors have proposed a unifying function for this area: a ‘circuit-breaker’ that interrupts ongoing activity, and redirects attention toward salient stimuli (Corbetta and Shulman, 2002), a ‘nexus’ area where low-level cognitive processes integrate to bring about higher-level functions (Carter and Huettel, 2013), an area that computes representations about other people’s awareness and the observer’s own awareness (Graziano and Kastner, 2011), a processor of contextual updating (Danckert et al., 2012; Geng and Vossel, 2013), a predictive processing machine (Masina et al., 2022) or a detector of mismatches between expected and actual sensory, motor, or cognitive events (Doricchi et al., 2022, 2010). Cabeza et al. (2012) have, after considering

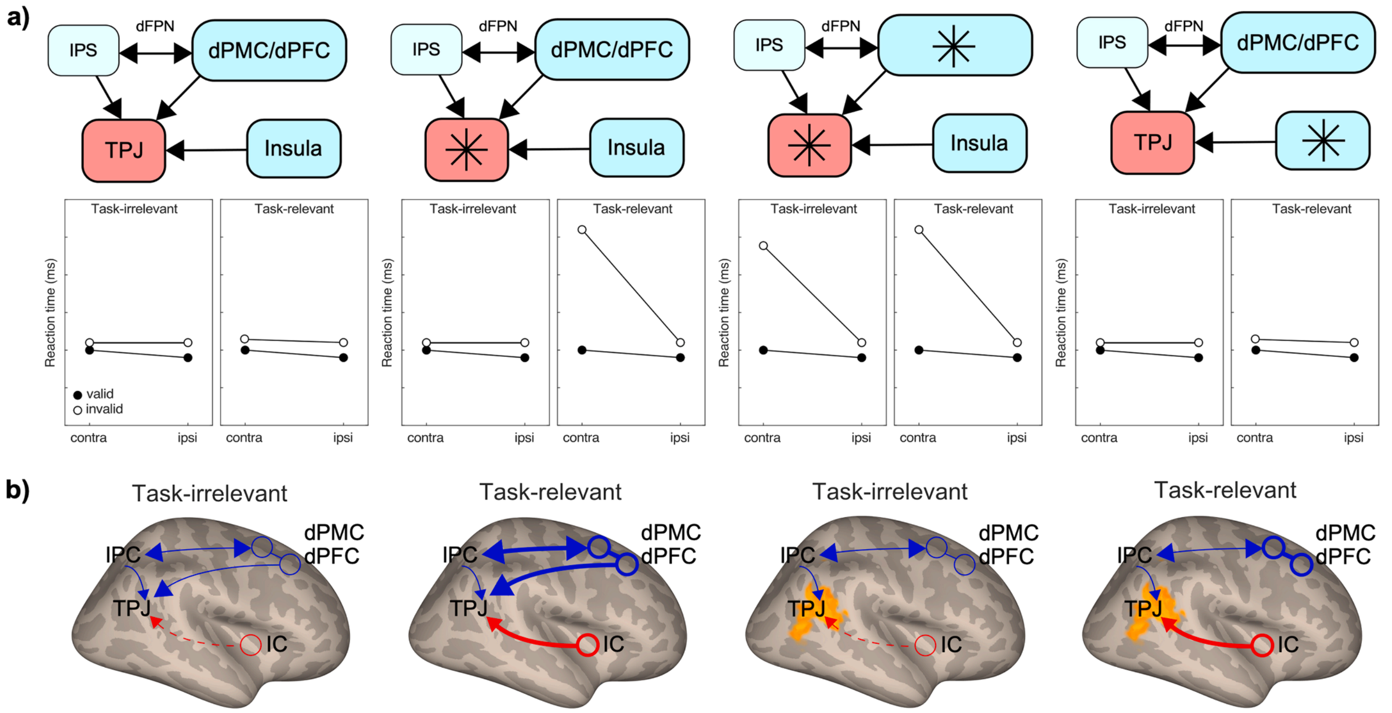

Fig. 6. Anatomical model of the disengagement deficit. a) Different scenarios showing the effects of complete preservation (first panel) and damage to the temporo-parietal junction (TPJ; second panel), combined damage to the TPJ and dorsal premotor and prefrontal cortex (dPMC/dPFC; third panel), or damage to the insula (fourth panel). The disengagement deficit is confined to task-relevant cues when only the TPJ is damaged, while it is observed for all cue types after combined damage to the TPJ and the dPMC/dPFC. Lesions of the insula do not, or only moderately affect attentional disengagement (dFPN: dorsal frontoparietal network). b) Functional interactions between regions of the right-hemispheric attention network that affect attentional disengagement. The orienting response of the TPJ toward task-irrelevant and task-relevant cues is modulated by dorsal frontoparietal cortex (dPMC/dPFC and intraparietal cortex, IPC) and the insular cortex (IC). In the healthy brain (left) the incoming modulatory signals are equally strong and therefore cancel each other. After damage to the right TPJ and its functional disconnection from the dPMC/dPFC only weak modulatory signals from the IPC arrive at the TPJ. These are insufficient to compensate for the strong, saliency-driven modulation by the insula.

various theoretical hypotheses, concluded that an attentional framework provides the most comprehensive and parsimonious explanation for the TPJ's cognitive function. They posit that the TPJ plays a major role in detecting and automatically orienting attention toward salient stimuli in the environment or salient internal signals. The lesion studies discussed in Section 4.9 largely align with this view, in particular where they indicate that the disengagement deficit after TPJ damage is notably influenced by the behavioral relevance of the cue (Pedrazzini and Ptak, 2019; Ptak and Pedrazzini, 2021). Thus, while the right TPJ appears to redirect attention to salient or unexpected stimuli, it demonstrates particularly heightened sensitivity to task-relevant information.

It is important to recognize that the significance of task relevance does not contradict the initial depiction of the disengagement deficit in the classic Posner task (Posner et al., 1984). In this particular version of the spatial cueing task, both cue and target share at least two key properties: color and abrupt appearance, with a neutral (task-irrelevant) condition being absent. Consequently, because patients are instructed to respond to a suddenly appearing peripheral target, and the cues are presented at one of the two potential target locations, their abrupt appearance elicits a rapid and transient response from the TPJ. Further, it is important not to confuse task relevance with action relevance, as cues do not necessitate any action from the observer. Patients are explicitly instructed to disregard the cues and only respond to the target. This instruction is well-followed, with patients producing similar numbers of false positive responses to the cue as healthy participants (Pedrazzini and Ptak, 2019).

Another crucial brain region contributing to the disengagement effect is the dPMC/dPFC. Damage to this region results in reduced responses to contralateral visual stimuli and distinct modulations of early electrocortical activity, suggesting that this region modulates visual processing through intrahemispheric fronto-occipital and fronto-temporal connections (Barcelo et al., 2000). More notably, such damage eliminates the effect of task-relevance on the disengagement deficit, while patients retain a general disengagement deficit with all cue types (Ptak and Schnider, 2010). Additionally, the connectivity between the right dPMC/dPFC and the posterior parietal cortex predicts the impact of task-relevant distractors on attentional processing, both in healthy participants and patients with spatial neglect (Fellrath et al., 2016). Furthermore, a functional disconnection of the dPFC and the TPJ is associated with an increased disengagement deficit with task-relevant cues (Ptak and Pedrazzini, 2021).

Based on these findings, we propose that the dPMC/dPFC plays a pivotal role in modulating responses in downstream areas by temporarily amplifying the perceived saliency of a task-relevant stimulus. The amplification of sensory signals is a well-known property of spatial attention, which has been linked to response characteristics of the dorsal fronto-parietal cortex, in particular the IPC (Constantinidis and Steinmetz, 2001; Gottlieb et al., 1998) and the frontal eye field (FEF; Bichot and Schall, 1999; Fecteau and Munoz, 2006). Neuroimaging studies have also demonstrated that the IPC and FEF, along with the dPMC/dPFC, exhibit the strongest activations among any brain region when a task requires subjects to maintain information in working memory (Gazzaley and Nobre, 2012; Koenigs et al., 2009; Li et al., 2022; Owen et al., 2005).

Similar to the dPMC, the IPC responds transiently when attention selects stimuli based on reflexive or voluntary processes, suggesting that it computes attentional priority by integrating sensory and higher-order cognitive properties of environmental stimuli (Bisley and Goldberg, 2010; Serences and Yantis, 2007; Yantis et al., 2002). Consequently, the role of the frontoparietal cortex in amplifying task-relevant sensory features of stimuli hinges on its capacity to maintain and update action goals in response to changing task requirements (Knudsen, 2007). This function of the frontoparietal cortex also offers an explanation for why the TPJ displays strong sensitivity to task relevance when functionally disconnected from the dPMC but exhibits no sensitivity when the dPMC is damaged. In cases of disconnection between the dPMC and the TPJ, information about task relevance is relayed indirectly to the TPJ via the IPC, though this relay may weaken the modulating influence of the dorsal frontoparietal network on the TPJ. If the dPMC/dPFC is damaged, task-relevant properties are not correctly encoded (or are not maintained), resulting in a failure to capture attention.

The third brain region in the triangular model is the right insula, which serves as a central component of a 'saliency network' consisting of the insula, the amygdala, and anterior cingulate cortex, which is activated in response to salient external or internal stimuli (Seeley et al., 2007). The insula exhibits sensitivity to a wide range of biologically relevant signals associated with visceral stimulation, emotions, or pain. It interacts with attention networks by modulating the priority of motivationally relevant information (Menon and Uddin, 2010; Uddin, 2015). Functionally, the insula is connected with the anterior part of the TPJ (Mars et al., 2012). A recent lesion study suggested that the right insula contributes to neglect symptoms as a functional 'hub' that connects, and possibly integrates emotional, motivational and perceptual signals through connections with the amygdala, the inferior frontal gyrus, and the occipital lobe (Wiesen et al., 2022). However, in contrast to the TPJ, isolated damage to the insula does not lead to an increased impact of task-relevant cues on spatial attention (Pedrazzini and Ptak, 2019). This finding suggests that this region does not directly encode or maintain the task-defining characteristics in the form of an action goal. Instead, the insula appears to bias attention, possibly by adding motivational value to those characteristics. This role of the insula can also explain the finding that cues with negative reward capture attention in neglect similarly to task-relevant cues (Bourgeois et al., 2022), suggesting an impact of motivational codes on spatial attention.

It is important to note that this model is specifically designed to explain the effects of attentional capture and the failure of disengagement in patients with focal brain damage. It is not intended to provide a comprehensive description of the findings of functional imaging studies and is limited by anatomical constraints and the shortcomings of lesion analysis methods. For example, knowledge about the functional role of the IPC is based on a limited number of patients, often with bilateral lesions. This region is situated at the border between two vascular areas, and isolated damage to the IPC is rare (Gillebert et al., 2011; Pedrazzini et al., 2016). Due to issues regarding statistical power modern lesion-symptom mapping technique often exclude rarely involved brain regions from the analysis (Sperber and Karnath, 2018). A similar problem applies to the specific role of the FEF, which has mainly been studied with regard to its role in saccade planning, not spatial attention (Machado and Rafal, 2004). Another challenge is that many studies using the spatial cueing paradigm have examined small groups of participants, which do not allow for systematic examination of identifiable components of attention networks. These are important caveats that restrict the extent of conclusions that can be drawn from an anatomical model which is essentially based on lesion studies. Confirmation and refinement of this model require rigorous testing of distinct patient groups with damage to specific brain regions. This further necessitates measures of functional interactions between these brain regions, such as with assessment of functional connectivity. The combination of lesion methods with functional neuroimaging, as has been done in some recent studies, is the most promising way to identify the anatomical foundations of spatial attention deficits.

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