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Research Report

Neglect symptoms are related to a prediction-hypersensitivity in ipsilesional space

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ABSTRACT

The precise cognitive mechanisms underlying spatial neglect are not fully understood. Recent studies have provided the first evidence for aberrant behavioral and electrophysiological prediction and prediction error responses in patients with neglect, but also in right-hemispheric (RH) stroke patients *without* neglect. For prediction-dependent attention, as assessed with Posner-type cueing paradigms with volatile cue-target contingencies, studies in healthy volunteers point to a crucial role of the right temporo-parietal junction (rTPJ) – as part of a network commonly disrupted in neglect. In order to study altered prediction-dependent attention in patients with RH damage and neglect, the present study employed a spatial cueing paradigm with unsignalled changes in the cue's predictive value in 26 RH patients, 21 left-hemispheric (LH) patients, and 33 healthy elderly controls. The inference of the changing cue's predictive value was assessed with a Rescorla-Wagner learning model of response times (RTs) and participants' ratings. We tested for lesion-side-dependent relationships between the computational model parameters, ratings, and neuropsychological performance. Moreover, we investigated links between the behavioral signatures of predictive processing and lesion anatomy (lesion location and disconnection). The results provided no evidence for a predictive inference deficit, but revealed a correlation between a hypersensitivity of RTs to inferred predictions for ipsilesional stimuli and neglect symptoms in RH patients. Irrespective of symptoms of neglect, the rating of the cue's predictive value deviated more from the actual values in RH patients. RT hypersensitivity for ipsilesional targets was linked to disconnection within fronto-parietal, fronto-occipital, and temporo-parietal pathways. These findings provide novel insights into the role of altered prediction-dependent processing for neglect as assessed by different read-outs, highlighting an exaggerated response adaption to predictions of ipsilesional stimuli.

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1. Introduction

Spatial neglect is characterized by a failure to detect and respond to contralesional stimuli. Basic sensory or motoric problems cannot explain this impairment, which has traditionally been attributed to attentional and representational deficits in contralesional space. Neglect is more prevalent after right-hemispheric (RH) than after left-hemispheric (LH) brain damage (Beis et al., 2004). While it can be observed after lesions to various brain regions, inferior parietal and temporo-parietal lesions, as well as damage to fronto-parietal white matter tracts, such as the superior longitudinal fasciculi (SLF), play critical roles in core symptoms of neglect (Lunven & Bartolomeo, 2017; Thiebaut de Schotten et al., 2014).

Besides attentional deficits, it is debated whether neglect is associated with impairments in processing statistical regularities and in maintaining and updating predictive internal models. Earlier studies suggested that neglect patients can learn the probability of target locations to improve their performance in contralesional space (Geng & Behrmann, 2002, 2006) and can use predictive cues to facilitate attentional orienting (Bartolomeo et al., 2001; Wansard et al., 2015). Shaqiri and Anderson (2012, 2013) observed that RH stroke patients (with and without neglect) showed reduced priming for repeated stimulus positions. The patients' responses were still affected by the probability distribution of the stimuli, although to a lesser degree than in healthy controls. A computer version of the "rock, paper, scissors"-game was used to investigate the adaptation of choice behavior to a strategy change of a computer opponent in RH and LH patients (Danckert et al., 2012). Unlike healthy controls and LH patients, RH patients did not correctly adjust their choice behavior when the computer departed from uniform play. As in previous studies (Shaqiri & Anderson, 2012, 2013), these deficits could not unequivocally be related to neglect in the RH group. A lesion analysis implicated the insula and the putamen in this deficit (Danckert et al., 2012).

In contrast to these findings, recent EEG studies have provided the first evidence for neglect-specific alterations of cortical updating and novelty responses. In a spatial cueing paradigm, neglect patients exhibited an exaggerated novelty (P3a component) response to ipsilesional targets, a reduced novelty (P3a) response to contralesional targets, and impaired contextual updating (P3b) in contralesional space (Lasaponara et al., 2018). Doricchi et al. (2021) employed an auditory oddball paradigm and observed double dissociations between the mismatch negativity and P3 responses in ipsi- and contralesional space, suggesting that predictive processing in neglect is exclusively based on statistical regularities of ipsilesional events. Another study revealed that neglect patients exhibit abnormal contingent negative variation (CNV) responses for predictive left and right cues (Lasaponara et al., 2020). A suppressed (more positive) CNV component to ipsilesional cues was associated with more severe neglect in the line bisection task, leading to the notion that neglect may be characterized by an abnormally sustained expectation of stimuli in ipsilesional hemispace. Besides these empirical studies, theoretical modeling work has linked disconnection within a synthetic subcortico-fronto-parietal network to different computational mechanisms leading to a biased saccadic sampling of space in neglect (Parr & Friston, 2018).

Imaging and neurostimulation studies in healthy participants have shed light on the brain structures and networks supporting prediction- and updating-related attentive processing. In spatial cueing tasks with central symbolic cues, manipulations of the proportion of validly and invalidly cued trials (i.e., the cue's predictive value) affect both the behavioral cueing effects as well as electrophysiological and neuroimaging signatures of attentional orienting and reorienting (e.g., Lasaponara et al., 2011; Vossel et al., 2012). Applications of formal learning models such as the Rescorla-Wagner model (Rescorla & Wagner, 1972) or the Hierarchical Gaussian Filter (HGF, Mathys et al., 2011) to response times (RTs) have provided evidence that healthy participants infer the trial-wise predictive value of the cue based on recent observations. fMRI studies have shown that activity in rTPJ is modulated by the trial-wise predictive value derived from such models, in that the response in this region decreases in valid and increases in invalid trials with higher estimated predictive value of the cue (Vossel et al., 2015). Disruption of rTPJ by online TMS slows the learning of the actual cue's predictive value when TMS is applied 300–500 msec after the target appearance (Mengotti et al., 2017). Results from a combined offline TMS-fMRI study have suggested that the connectivity between rTPJ and the right insula plays a role in this TMS-mediated behavioral effect of rTPJ (Mengotti et al., 2022). These findings align with proposals that rTPJ is involved in contextual updating (Geng & Vossel, 2013) and acts as a mismatch detector across multiple cognitive domains in the human brain (Doricchi et al., 2022).

Taken together, previous findings have provided the first evidence for altered prediction-dependent processing in contralesional but also ipsilesional space in patients with neglect. Still, deficits in predictive behavior have also been observed in non-spatial tasks and RH patients without neglect. Hence, it remains to be investigated if and how stroke-induced impairments of these processes contribute to the neglect syndrome. Existing studies have either employed tasks in which predictive processing is reflected in RTs or electrophysiological responses (as in oddball or spatial cueing tasks) or tasks involving explicit choices (as in the "rock, paper, scissors"-game). Therefore, it is unclear if similar impairments are observed in more implicit or explicit measures of predictive processing.

Our study investigated RH and LH stroke patients and healthy elderly volunteers using a spatial cueing task with changes of the cue's predictive value to address these open questions. The task was a simplified version of tasks employed in the fMRI and TMS studies showing a crucial involvement of rTPJ (Mengotti et al., 2017; Vossel et al., 2015). A Rescorla Wagner (RW) learning model combined with a response model based on RTs was employed to quantify the participants' inference about the cue's predictive value and its impact on behavior. Additionally, participants were asked to provide explicit ratings of the cue's predictive value during the task. All patients were tested for the presence of neglect, aphasia, and apraxia. Parameters derived from the modeling of RTs and explicit ratings were investigated concerning performance in these neuropsychological tests, lesion location,

and disconnection patterns. We hypothesized that symptoms of neglect and direct or indirect damage (disconnection) to rTPJ should be associated with deficient predictive processing in this task. We tested if these deficits concerned i) updating of predictions after new observations (as reflected in model-derived RW-learning rates for ipsi- and contralesional outcomes), ii) aberrant adaption of responses to inferred predictions (as reflected in parameters of the RT response model), or iii) explicit ratings of the cue's predictive value.

2. Methods

No part of the study procedures and/or study analyses was pre-registered in a time-stamped, institutional registry prior to the research being conducted.

2.1. Study sample

To be enrolled in the study, patients had to fulfill the following inclusion criteria: age between 18 and 90 years, sufficient knowledge of German, no signs of dementia, no alcohol or drug abuse, no previous history of other neurological or psychiatric diseases, ability to give written consent, ability to perform computerized attention-demanding tasks, first-ever unilateral stroke, and no severe aphasia (precluding understanding of the task instructions). Moreover, patients were asked before the start of the task if they could perceive the peripheral stimuli while fixating on the central diamond as a practical approach to avoid that performance was affected by visual field defects. One hundred and six patients were screened for participation in the experiment. Forty-eight of these patients fulfilled the inclusion criteria (mean age 56.4 years old, range: 24–77; male/female: 27/21; mean days post-stroke 116.1 days, range 15–674; 41 ischemic and 7 hemorrhagic strokes; mean MMSE score 28.9, range 24–30). The two most common reasons for exclusions were the inability to perform the computerized task and evidence of white matter disease grade 3 (Fazekas et al., 1987) or presence of an older stroke. The reasons for being unable to perform the task were related to insufficient understanding of the task instructions or to discontinuing the task after a few trials due to exhaustion. No patient had to be excluded because the peripheral stimuli could not be perceived. Out of the 48 included patients, 22 patients suffered from LH stroke (mean age 53.9 years old, range: 24–77; male/female: 12/10; mean days post-stroke 165.5 days, range: 20–674; mean MMSE score 29.0, range 26–30) and 26 patients suffered from RH stroke (mean age 58.5 years old, range: 28–76; male/female: 15/11; mean days post-stroke 74.3 days, range: 15–469; mean MMSE score 28.8, range 24–30). Since cancellation test data could not be obtained for 1 RH patient, correlation analyses with neuropsychological neglect test performance were conducted with 25 RH patients. Moreover, another RH patient did not complete the apraxia test. Data from one LH patient was discarded from the performance analyses in the experimental cueing paradigm due to 100% and 88% missed responses in two conditions, so that here data from 21 LH patients could be analysed. Age, time post-stroke, MMSE scores, and the number of lesioned or disconnected voxels did not differ significantly between LH and RH patients.

Due to the correlational approach of the study, we did not employ any cut-offs to classify our patients about the presence or absence of neglect for the main analyses. The present sample size is comparable to a study that revealed differences in model parameters in similar cueing tasks in different age groups comprising $n = 20$ participants each (Mengotti, Kuhns, et al., 2020), as well as to the EEG study, which observed a significant correlation with neglect symptoms in 25 RH stroke patients (Lasaponara et al., 2020). For completeness, significant correlational analyses with neglect test performance were additionally followed up by comparisons between patients scoring below and above cut-off scores of the neuropsychological neglect tests within the RH group.

Besides, 35 healthy elderly (>50 years old) control (HC) participants without a history of neurological or psychiatric disease participated in the study. Due to a technical error in one participant and abortion of the task in another participant, the final sample comprised 33 control participants (mean age 63.4 years old, range: 51–80; 19 female; MMSE = 30 for all participants).

All patients and control participants gave their written informed consent before participating in the study. The study was conducted under the ethical principles of the World Medical Association (Declaration of Helsinki) and approved by the ethics committee of the Medical Faculty of the University of Cologne (reference number 13-383).

2.2. Procedure

Due to the limited attention span of the patients, the neuropsychological assessment and the experimental paradigms were carried out on multiple days; controls performed all tests and experimental paradigms on the same day. All participants performed two additional versions of the task, in which the cue either indicated the color of the target stimulus or the motor response to the target stimulus, respectively. The order of task administration was counterbalanced. The present analyses focus on the data from the spatial cueing task only.

2.3. Neuropsychological tests for stroke-related impairments and principal component analysis

For the assessment of visuospatial neglect, the stroke patients performed standardized paper-and-pencil tests from the Neglect Test (NET; Fels & Geissner, 1997), an adapted version of the Behavioural Inattention Test (Wilson et al., 1987). The NET subtests letter cancellation, star cancellation, figure copying, reading, and clock drawing were employed. Furthermore, the random symbol version of the Mesulam Weintraub Cancellation task (Weintraub & Mesulam, 1988) and the Landmark-M task (Bisiach et al., 1998) were conducted. In order to quantify the spatial bias in the cancellation tasks, a laterality index was calculated according to the following formula: LI = (hits contralesional−hits ipsilesional)/(hits contralesional + hits ipsilesional) (Bartolomeo & Chokron, 1999; Marshall et al., 1975). This index can vary between −1 and +1, with a score of −1 reflecting a complete omission of all letters in the contralesional hemifield and a score of +1 reflecting a complete omission of all letters in the ipsilesional hemifield. A score of 0 indicates an equal amount

of canceled letters in both hemifields. In the Landmark-M test (Bisiach et al., 1998), patients were presented with nine bisected lines and asked to manually point with their ipsilesional hand to the longer or shorter segment in different blocks of trials. The Landmark-M task yields two indices for perceptual bias (PB) and response bias (RB), i.e., perceptual and motor-intentional neglect symptoms. For both PB and RB, a value of 50 indicates no spatial bias. Here, we quantified the deviation of the patients' PB and RB scores from 50 and transformed the scores so that negative deviations reflect stronger contralesional biases for both LH and RH patients. Extinction was assessed clinically with the visual confrontation technique.

Aphasic symptoms were assessed with a short form of the aphasia checklist (ACL-K; Kalbe et al., 2002). For the assessment of apraxia, the Cologne Apraxia Screening was applied (KAS for LH patients, Weiss et al., 2013; KAS-R for RH patients, Wirth et al., 2016). Since KAS and KAS-R use a different number of items (in addition to mirrored stimuli), we transformed the absolute scores into relative scores by dividing them by the maximum score (80 *vs* 48 for KAS and KAS-R, respectively) and multiplying by 100.

Supplementary Table S1 provides an overview of the performance in all neuropsychological tests with quantitative scores in both patient groups. Supplementary Table S2 shows the neuropsychological results in the RH group separately for patients performing below and above cutoff-scores of the neglect tests. In the LH group, only one patient showed an above-cutoff RB score for contralesional motor-intentional neglect.

For dimensionality reduction, the results from neuropsychological tests with quantitative scores (laterality indices of the three cancellation tasks, PB and RB of the Landmark-M test, scores of ACL-K and KAS) were subjected to a principal component analysis (PCA) with varimax rotation. An eigenvalue >1 was used to extract the components. Note that for all scores or indices, smaller values reflect worse performance or stronger contralesional neglect, respectively. To assess the suitability of the data for PCA, the Bartlett test of sphericity was employed. This test was significant ($\chi^2 = 90.77$, $p < .001$), indicating that the correlation matrix was different from an identity matrix. Moreover, the Kaiser-Meyer-Olkin (KMO) measure amounted to .545, which is above the critical cutoff of .5 (Hair, Black, Babin, & Anderson, 2006; Kaiser, 1974). Still, given the low KMO value, we repeated the PCA without the star cancellation test, which did not show a lateralized impairment in more than 70% of the patients. The PCA with six tests yielded a KMO value of .633 and produced the equivalent component structure. To reduce the dependency of the individual component scores on the specific component loadings (which may be more sample-specific), we averaged the Z-score of each test with a unique and high loading on the respective component (cf. Supplementary Table S3). Thereby, we could also keep the data from participants with missing tests for the other components.

2.4. *Experimental paradigm*

Participants performed a modified spatial cueing paradigm (Posner, 1980) with central cues (see Fig. 1 A) programmed in Presentation (Neurobehavioural Systems). This paradigm was a simplified version of the task used in previous imaging and neurostimulation studies in healthy volunteers from which our hypotheses were derived. Although attentional deficits in neglect patients may be more pronounced in exogenous cueing tasks with peripheral cues and short cue-target intervals, these paradigms test automatic (stimulus-driven) attention (or a combination of automatic and voluntary attention in case of predictive cues) and are hence less suited to specifically assess the top-down guided allocation of attention by inferred predictions, which was the focus of this and previous studies. The relatively long cue-target interval (200 msec longer than in Mengotti et al., 2017) was used to ensure that patients had enough time to process the cue and to voluntarily orient attention in space (note that in contrast to peripheral cues, central symbolic cues do not induce inhibition of return). Participants were asked to respond to a left or right target stimulus (red or blue triangle presented with ~7.6° eccentricity from fixation) and to indicate whether it pointed upwards or downwards by button presses with the index or middle finger, respectively. This ensured that participants indeed perceived and processed the target correctly (which can be difficult in simple detection tasks unless variable cue-target intervals or catch trials are used). The stimulus-response mapping (upward-pointing/downward-pointing triangle–index/middle finger) was counterbalanced across participants. Patients responded with their unaffected (ipsilesional) hand. In the group of 33 healthy volunteers, 17 responded with their right and 16 with their left hand. Before the start of the main task, participants completed a practice run with a constant .75 predictive value of the cue. The main task consisted of three blocks, each comprising 80 trials. This block length was longer than in the previous studies to ensure that the different predictive values could be inferred from the observations. The probability of the cue being valid (i.e., the cue's predictive value, CP) was manipulated across the different blocks, amounting to .8, .4, and .6 (see Fig. 1D). In each block, left and right targets were equally likely and were counterbalanced across valid and invalid conditions. The block and trial order was identical for all participants. This procedure is common in computational inference studies on conditional probabilities to ensure that model parameter differences can be attributed to participant-specific rather than task-specific factors, and to rule out that different carry-over effects between blocks affect the results. Participants were not informed about the CP levels, but they were informed that the CP level could change between blocks. After each block, they were asked to provide an explicit rating of the percentage of valid cues (see Fig. 1B).

2.5. *Statistical analysis of behavioral data*

Data preprocessing and modeling was performed with MATLAB (MathWorks). Statistical analyses of behavior at the group level were performed in SPSS 25 (IBM) and JASP .17.1 (JASP Team, 2023) for classical and Bayesian statistics, respectively.

2.5.1. *General task performance*

RTs faster than 100 msec were discarded from all analyses. To compare general task performance across groups as a

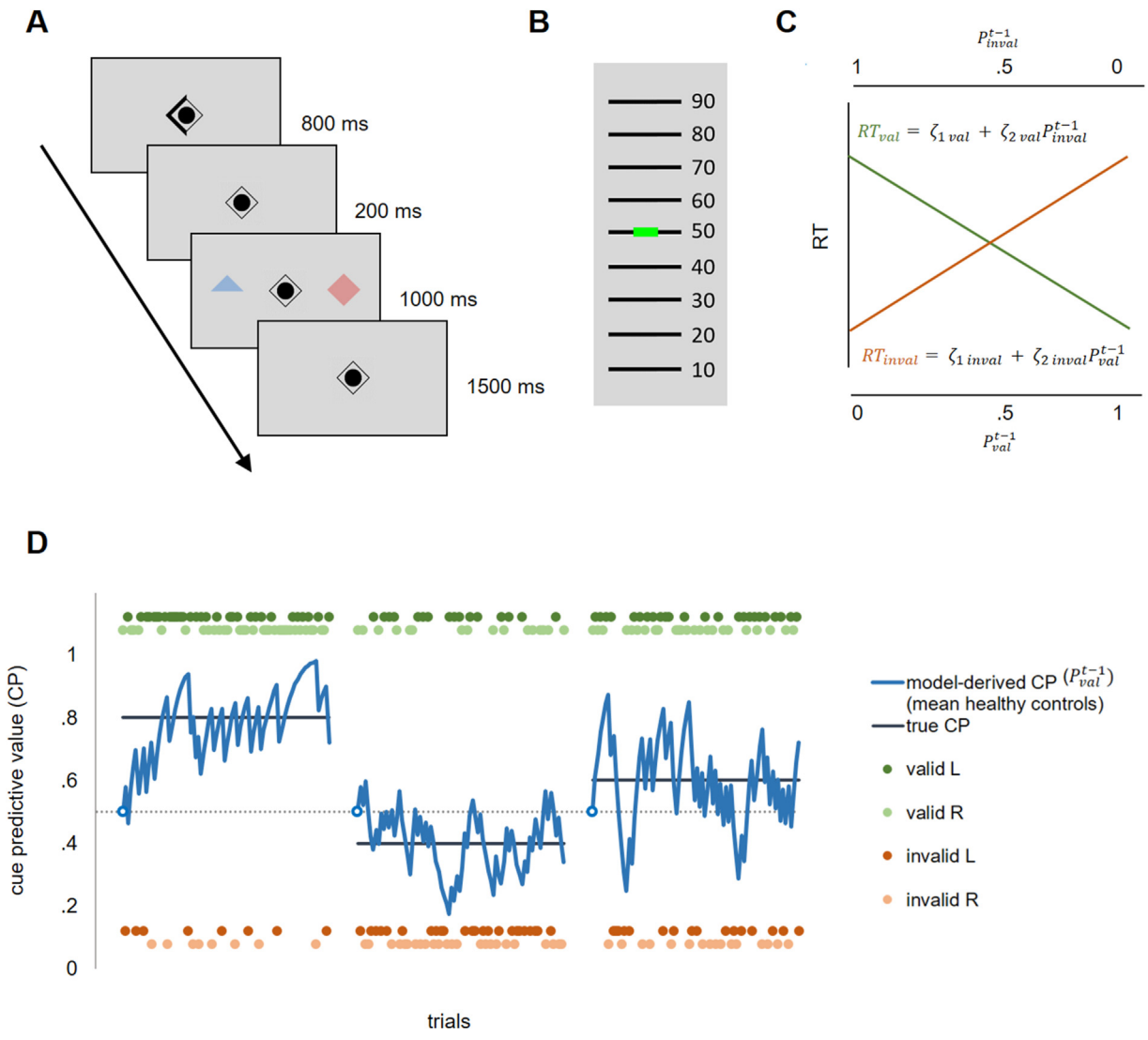

Fig. 1 – A) Illustration of the spatial cueing paradigm. An example of a validly cued left target is shown. Participants were asked to indicate by button press with the index or middle finger of one hand whether the target triangle was pointing up- or downward. The distractor diamond in the opposite hemifield was irrelevant to the participant's task. B) After each block, participants were asked to provide an explicit estimate of the predictive values of the cue (in %) on a rating scale. C) Illustration of the response model according to which RTs vary linearly with the model-derived predictive value of the cue (CP). RTs in invalid trials (orange line) were assumed to increase with increasing probability of the cue being valid (P^{t-1}_{val}, depicted on the lower *x*-axis), i.e., when invalid trials are more unexpected. Conversely, RTs in valid trials (green line) were supposed to increase with the probability of the cue being invalid ($P^{t-1}_{inval} = 1 - P^{t-1}_{val}$, depicted on the upper *x*-axis in reverse order). The ζ_2 parameter describes the slope of the linear function in valid and invalid trials. Note that the pattern in these graphs schematically illustrates the rationale of the response model, but that parameters were estimated separately for left and right valid and invalid trials to allow for hemifield and validity-specific differences (see main text). D) Illustration of the trial sequence, the block-wise manipulation of the cue's predictive value (CP), and the model-derived estimate of CP (as derived from the mean learning rate of the group of healthy controls).

function of target hemifield, mean response time (RT) and accuracy for left and right targets entered 2 × 3 ANOVAs with the within-subject factor *hemifield* (left/right) and the between-subject factor *group* (HC/LH/RH). Post-hoc *t*-tests followed up significant interactions. Additionally, we compared the percentage of left and right omissions (targets with no responses) between the three groups with a further 2 × 3 ANOVA.

2.5.2. *Model-free analyses of validity effects in RTs*

As a first step, the effect of the experimental manipulation of the cue's predictive value (CP) on validity effects (VE = mean RT invalid minus mean RT valid) was calculated for each participant and block, separately for left and right targets. This way, we tested if participants learned the different cue-target contingencies, i.e., allowing for applying a formal learning model of RTs in a subsequent step. For this analysis, the first 8

trials of each block were discarded to capture better the effect of the cue's predictive value, which needed to be inferred by the participants from trial-wise observations. A 2 × 3 × 3 ANOVA with the within-subject factors *hemifield* (left/right) and CP (.8/.6/.4) and the between-subject factor *group* (HC/LH/RH) was performed to investigate the modulation of the VE as a function of the cue's predictive value and hemifield. Greenhouse-Geisser correction of degrees of freedom was applied when the Mauchly test signaled a violation of the sphericity assumption. In healthy controls, VEs were expected to increase with higher CP, since invalid trials are less expected and valid trials are more expected with a higher probability of the cue being valid.

2.5.3. *Estimation of learning model parameters based upon RTs*

All modeling analyses were performed using the HGF functions within the TAPAS toolbox (http://www.translationalneuromodeling.org/tapas/; Frässle et al., 2021) running on MATLAB. The Rescorla Wagner (RW) rule was applied to trial-wise RT to describe the evolvement of a participant's belief about the probability of the cue being valid from trial to trial (Mengotti et al., 2017). This approach yields participant-specific parameters that directly reflect belief updating about the cue's predictive value (CP) after new observations and the strength of the modulation of RTs by the inferred CP. We used a simple RW learning scheme (instead of the hierarchical HGF model in which updating additionally depends on higher-level beliefs about volatility) since our paradigm consisted of blocks with constant block length and, therefore, did not include a manipulation of higher-level volatility (with more stable and more volatile phases). In particular, the participants in the present task observed a binary trial-wise outcome u, which could be either a valid target ($u = 1$) or an invalid target ($u = 0$) presented on the left ($s = 0$) or right ($s = 1$) side. After the observation of the outcome of a trial (t), the probability of a valid cue (P^t_{val}) is derived from the prediction error in this trial (δ^t)—which is weighted by the learning rate α—and the estimate from the previous trial (P^{t-1}_{val}). In this task, separate values for α (α_L or a_R) were estimated for trials with left and right targets to allow assessing hemifield-specific differences in updating behavior:

$$P^t_{val} = \begin{cases} P^{t-1}_{val} + \alpha_L \delta^t & for\ s^t = 0 \\ P^{t-1}_{val} + \alpha_R \delta^t & for\ s^t = 1 \end{cases} \quad (1)$$

with $\delta^t = u^t - P^{t-1}_{val}$ and $u \in \{0|1\}$

Hence, the learning rate α determines the impact of prediction errors and reflects how the discrepancy between the observed and predicted outcome triggers the updating of predictions from trial to trial. Before observing any experimental trials, the prior belief (P^0_{val}) was set .5 for each of the three blocks, and the model parameters were estimated separately for each block. An alternative possibility would be that participants do not start with a neutral expectation for each task block but hold on to the belief about P^t_{val} from the preceding block. Fitting the model with individual P^0_{val}-values derived from the last trial of the preceding block for blocks 2 and 3 yielded highly similar model parameters (correlations ranging from .87 to .98), indicating that the choice of the starting value did not have a substantial impact. Since a P^0_{val} of .5 was more congruent with the task instructions that the cue's predictive value could change and does not depend on individual prior estimation outcomes, we used this value for the estimations. Fig. 1D (blue line) shows an example of the evolvement of beliefs about the cue's predictive value based on the mean learning rates in the control group.

The RW learning model was combined with a response model (Daunizeau et al., 2010), specifying the relationship between the inferred predictive value of the cue and RTs (see Fig. 1C). Similar as in previous work (Mengotti et al., 2017, 2022; Mengotti, Kuhns, et al., 2020), we assumed linear relationships between RTs and the expected predictive value of the cue at the beginning of trial t (i.e., before the observation in trial t; P^{t-1}_{val} and $P^{t-1}_{inval} = 1 - P^{t-1}_{val}$). In invalid trials, RTs were assumed to increase with increasing predictive value P^{t-1}_{val}, so that RTs are slower when valid trials are more (and invalid trials are less) expected. Conversely, RTs were assumed to increase with $P^{t-1}_{inval} = 1 - P^{t-1}_{val}$ in valid trials. To allow for hemifield- and validity-specific differences, separate response model parameters were estimated for left and right valid and invalid trials:

$$RT^t = \begin{cases} \zeta_{1val\_L} + \zeta_{2val\_L} P^{t-1}_{inval} & for\ u^t = 1\ and\ s^t = 0 \\ \zeta_{1val\_R} + \zeta_{2val\_R} P^{t-1}_{inval} & for\ u^t = 1\ and\ s^t = 1 \\ \zeta_{1inval\_L} + \zeta_{2inval\_L} P^{t-1}_{val} & for\ u^t = 0\ and\ s^t = 0 \\ \zeta_{1inval\_R} + \zeta_{2inval\_R} P^{t-1}_{val} & for\ u^t = 0\ and\ s^t = 1 \end{cases} \quad (2)$$

The response model parameters ζ_1 and ζ_2 specify the intercept and slope of the linear function. Thereby, ζ_1 scales with the overall level of response times, and ζ_2 describes how much RTs change with changes in the inferred predictive value of the cue (Fig. 1C). Hemifield- and validity-specific response model parameters were implemented because RTs are known to be affected by both factors in RH patients and patients with neglect, often in an interactive fashion (e.g., Gillebert et al., 2011; Olk et al., 2010; Posner et al., 1984). Moreover, studies assessing learning of different predictive cue values have shown asymmetries, with a stronger modulation of RTs and neural activity in invalid than in valid trials (Dombert et al., 2016; Kuhns et al., 2017; Vossel et al., 2015).

Taken together, 10 parameters were estimated for each of the three CP-blocks (two learning model parameters: α_L and a_R, and eight response model parameters: ζ_{1val_L}; ζ_{1inval_L}; ζ_{1val_R}; ζ_{1inval_R}; ζ_{2val_L}; ζ_{2inval_L}; ζ_{2val_R}; ζ_{2inval_R}). Parameter estimation was performed using variational Bayes as implemented in the HGF toolbox (Frässle et al., 2021). Variational Bayes evaluates the posterior distribution of latent variables given the observed data based on analytical approximations to the posterior distribution (Bishop, 2006; Friston et al., 2007). For further analyses, the block-specific values were averaged. Learning rates did not significantly differ between the three blocks. The averaging procedure aimed at reducing noise of single blocks, while still taking into account general changes in RTs over time by the block-wise modelling.

Since ζ_1 is merely related to the overall response speed, the subsequent analyses focused only on those parameters that are related to prediction-dependent processes, i.e., on learning rates α and the ζ_2-parameters. In the first step,

hemifield- or validity-specific differences between the three groups were investigated with a 2 × 3 *hemifield* (left/right) × *group* (HC/LH/RH) ANOVA on α and a 2 × 2 × 3 *hemifield* (left/right) × *validity* (valid/invalid) × *group* (HC/LH/RH) ANOVA on ζ_2. These ANOVAs were followed up with Bayesian ANOVAs in JASP.

To test if altered updating or sensitivity of RTs to inferred CP contributed to neuropsychological performance, correlations between α- and ζ_2-values on the one hand, and the neuropsychological scores derived from PCA on the other hand were first assessed in the whole group of LH and RH patients. For these analyses, the learning/response model parameters were Z-transformed using the mean and standard deviation from the HC group to derive scores reflecting the deviation from normal behavior. The left and right hemifield scores were re-coded to reflect the ipsilesional and contralesional hemifield for each patient group. Thereby, we generated comparable scores for LH and RH patients, which reflected the deviation of the respective parameter from healthy controls. Since these correlation analyses were run separately for each of the four PCA components and each of the six learning/response model parameters, *P*-values were corrected for these 24 tests using the Bonferroni-Holm procedure (Holm, 1979).

Given the strong evidence for hemisphere-specific differences in the occurrence of cognitive deficits after stroke, moderator analyses were subsequently performed. These analyses tested if impairments in updating or behavioral adaptation to the inferred predictive cue value contributed to symptoms of neglect, apraxia, or aphasia—depending on the lesioned hemisphere (LH or RH). The Z-scores for each model parameter entered separate moderator analyses, using each of the four PCAs of the neuropsychological test performance as the dependent variable, the learning/response model parameter as the independent variable, and lesioned hemisphere as the moderator variable. These analyses were performed with PROCESS v4.1 in SPSS (Hayes, 2022). Again, *P*-values were corrected for 24 tests using the Bonferroni-Holm procedure. The analyses were followed up by Bayesian linear regression models performed in JASP to obtain Bayes factors (BF) for a model including the lesioned hemisphere × Z-scored model parameter interaction as compared to a null model including lesioned hemisphere and Z-scored model parameter as the only regressors.

To ensure that our modeling approach was able to identify learning rates (α-parameters) and RT sensitivity of inferred predictive values of the cue (ζ_2-parameters) independently, the posterior correlations of the two parameters were inspected (α_L and ζ_{2val_L}, ζ_{2inval_L}; α_R and ζ_{2val_R}, ζ_{2inval_R}). The group averages of the mean correlations across the three blocks were low and ranged between −.06 and −.13 in all three groups, suggesting that the parameters were indeed identifiable. Moreover, one-way ANOVAs revealed no significant differences in the posterior correlations between the three groups (all *P*-values >.38).

Besides these analyses of the parameters from a model estimating hemifield-specific learning rates and ζ_2-parameters, we estimated two reduced model versions and compared their model evidence with Bayesian model selection. One model contained only one learning rate for left and right targets, assuming that updating behavior would be identical in both hemispaces. The alternative model comprised hemifield-specific learning rates but only ζ_2 −parameters for valid and invalid trials in both hemifields. Random effects model selection using the spm_BMS.m function of the Statistical Parametric Mapping (SPM) software (Friston et al., 1995; Rigoux et al., 2014; Stephan et al., 2009) was employed to test if a model including laterality differences in updating or adaptation of RTs to inferred predictions provided more plausible explanations of the data. Furthermore, since the employed model comprised two different values for ζ_2 (for valid and invalid trials in the left and right hemispace), we also compared this model to a model with 4 (left/right × valid/invalid) α-values (and 4 ζ_2-values), and a model with 4 α-values and only 2 ζ_2-values for left and right targets. Again, random effects model selection was performed to test if the model with hemifield- and validity-specific α-parameters was superior to the initial model.

2.5.4. *Explicit ratings of the cue's predictive value*

For statistical analysis, the absolute discrepancy between the true (experimentally manipulated) and the explicit ratings of the cue's predictive value (see Fig. 1B) was calculated and averaged across all three CP blocks. The discrepancy scores were compared between the three groups with a one-way ANOVA followed up by Tukey-HSD tests. Again, correlations with the neuropsychological PCA scores were performed for the whole group, and moderator analyses were conducted to test if such relationships depended on the lesioned hemisphere. For both analyses, *P*-values were corrected for four tests using the Bonferroni-Holm procedure. To test if explicit ratings and more implicit measures of probability-dependent processing were related, correlations between Z-transformed discrepancy scores and learning/response model parameters were assessed, with Bonferroni Holm correction for six tests.

2.6. *Lesion and disconnection mapping and analyses*

Lesion mapping was performed using either MRI ($n = 40$) or CT ($n = 7$) clinical imaging data. Lesion boundaries were identified on a standard Montreal Neurological Institute (MNI) template using the freely available MRIcroN software. The clinical images were additionally normalized to MNI space with the Clinical Toolbox (Rorden et al., 2012) in SPM to support this transfer. Subsequently, the lesion contour was manually drawn onto the corresponding axial slices of the template (at 5 mm slice distance) based on the images in native and MNI space. This was done because the fully automated normalization yielded imprecise results in some of the patients. MRIcroGL was used to interpolate the lesion for the unmarked slices. Based on the individual lesion maps, additional probability maps of white matter disconnection were computed for each patient using the Disconnectome Maps tool of the Brain Connectivity and Behaviour (BCB) toolkit (https://github.com/chrisfoulon/BCBToolKitM; Foulon et al., 2018). Diffusion-weighted imaging data from 178 healthy controls of the Human Connectome Project (HCP) database was used (Thiebaut de Schotten et al., 2020) to track fibers passing through each patient's lesion. Patients' MNI space lesions were registered to each control native space and subsequently

used as the seed for the tractography in Trackvis (Wang & Wedeen, 2007). Tractographies from the lesions were brought to MNI space and used to produce a percentage overlap map by calculating the proportion of controls with a tract that crossed the lesioned area in each voxel. Thereby, the voxel-wise value considers the interindividual variability of tract reconstructions in controls and indicates a probability of disconnection from 0 to 100% for a given lesion (Thiebaut de Schotten et al., 2015). Before these maps entered group-level analyses, a threshold of 50% disconnection was applied (Billot et al., 2022).

Lesion and disconnection maps were used in subsequent multivariate group analyses (DeMarco & Turkeltaub, 2018; Zhang et al., 2014) to associate the model parameters of interest with the lesion anatomy. As in Billot et al. (2022), lesion and disconnection maps entered separate support vector regression (SVR) lesion-symptom mapping (LSM) or disconnection-symptom mapping (DSM) analyses, respectively. SVR-LSM/DSM analyses treat each voxel as the independent variable and a behavioral measure as the dependent variable in a multivariate regression. The beta value for each voxel indicates the strength of the relationship between this voxel and a predicted behavior (DeMarco & Turkeltaub, 2018). These analyses were performed with the SVRLSM toolbox running in MATLAB (https://github.com/atdemarco/svrlsmgui; DeMarco & Turkeltaub, 2018). Based on the hypotheses and the behavioral results, we tested for associations between lesioned or disconnected tissue and decreased contralateral learning rate Z_α_{contra}, increased ipsilesional RT sensitivity in valid trials $Z\_\zeta_{2val\_ipsi}$, and high deviation of the explicit rating from true CP in separate analyses, including patients of the RH group only (results of the SVR_LSM/DSM analyses with both LH and RH groups were highly similar and are provided in Supplementary Figure S3). Only voxels that were lesioned/disconnected in at least 5 patients were tested. A fivefold cross-validation of the SVR-beta maps was employed. The maps were thresholded using permutation testing with 10,000 permutations, a voxel-wise threshold of $p < .005$, and a cluster-wise correction at $p < .05$ (DeMarco & Turkeltaub, 2018). The analyses were additionally performed with the severity of neglect-like symptoms (PCA-derived scores) as a covariate for each variable of interest. For anatomical labeling of the DSM results, the resulting statistical maps were overlaid onto the probabilistic tractography atlas of white matter pathways from the Human Connectome Project (HCP; https://brain.labsolver.org/hcp_trk_atlas.html; Yeh, 2022) and the number of voxels within each tract (thresholded at 50% probability) was determined.

3. Results

3.1. Neuropsychological test performance

The PCA yielded four components with an eigenvalue >1, explaining 85.4% of the variance. The loadings of the different tests on the four components is provided in the Supplementary Table S3. Two of the cancellation tests loaded together with the perceptual bias score of the Landmark-M test on the first component, reflecting perceptual neglect of contralesional space. The response bias score of the Landmark-M test (reflecting motor-intentional neglect) and the apraxia test both loaded on a second component. The star cancellation test loaded on a third and the aphasia test on a fourth component. Supplementary Figure S1 shows the component scores (average Z-scores of contributing tests) of the individual patients from the LH and RH groups. Note that smaller values reflect more impairment. Table 1 provides mean average Z-scores for each component for the two groups. Mean scores for neglect component 1 were lower for RH than for LH patients. There were no significant differences between LH and RH patients for the other components. Time post-stroke did not correlate with the scores of PCAs1 to 3, but correlated negatively with PCA4-scores (reflecting worse performance in more chronic patients, $r = -.42$, $p = .003$).

3.2. General task performance

Mean (±sd) RT for the HC, LH and RH groups amounted to 765.56 (±140.61), 843.75 ± (±148.49) and 912.16 (±214.66) ms for left targets and 751.99 (±149.52), 852.20 (±150.07) and 871.88 (±189.13) ms for right targets. The 2 (*hemifield*: left/right) × 3 (*group*: HC/LH/RH) ANOVA on overall RT revealed significant main effects of *hemifield* [$F(1,77) = 7.83$; $p = .006$; $\eta_p^2 = .09$] and *group* [$F(2,77) = 5.0$; $p = .009$, $\eta_p^2 = .12$], as well as a significant *hemifield* × *group* interaction [$F(2,77) = 6.23$; $p = .003$; $\eta_p^2 = .14$]. This interaction was caused by a significant slowing of RTs for contralesional left as compared to ipsilesional right targets in the RH group [L-R difference 40.3 ± 56.6 msec; $t(25) = 3.63$; $p < .001$], which was not present in LH patients (L-R difference −8.44 ± 44.1 msec; $p = .390$) or the HC group (L-R difference 13.46 ± 41.2 msec; $p = .07$).

Mean (±sd) accuracy in the HC, LH, and RH groups amounted to 95.41 (±5.05), 92.74 (±6.62) and 92.22 (±10.40) % for left targets and 95.91 (±3.27), 93.27 (±6.16) and 93.17 (±7.89) % for right targets. The 2 (*hemifield*: left/right) × 3 (*group*: HC/LH/RH) ANOVA did not reveal any significant effects (all

Table 1 – Mean (±sd) scores for the neuropsychological tests contributing to each of the four principal components.

	LH	RH	
PCA1 (letter cancellation, MWCT, Landmark-M PB)[a]	.27 (±.26)	−.24 (±1.14)	$t(26.72) = 2.152$, $p = .041$
PCA2 (apraxia test, Landmark-RB)[a]	.14 (±.60)	−.13 (±.96)	$t(45) = 1.176$, $p = .246$
PCA3 (star cancellation)[a]	.0051 (±.46)	−.0045 (±1.3)	$t(31.21) = .34$, $p = .973$
PCA4 (aphasia test)	−.23 (±1.2)	.19 (±.76)	$t(34.37) = -1.43$, $p = .161$

[a] $n = 25$ RH patients.

$p > .160$). The percentage of omissions amounted to .35 (±.86), .56 (±1.16) and 1.92 (±3.91) % in the HC, LH and RH groups for left targets and .56 (±.99), 1.31 (±2.13) and 2.24 (±3.22) % for right targets. The ANOVA revealed significant main effects of *hemifield* [$F(1,77) = 6.6$; $p = .012$, $\eta_p^2 = .08$] and *group* [$F(2,77) = 4.1$; $p = .019$, $\eta_p^2 = .097$]. Omissions were higher for right than for left targets, and the post-hoc Tukey-HSD test revealed that RH patients showed significantly more omissions than HC ($p = .015$), with no significant difference to the LH group and between LH and HC groups ($p > .17$).

3.3. *Model-free analyses of validity effects in RTs*

The RTs and validity effects (VEs, RT invalid minus RT valid) for left and right targets in the three blocks with different experimentally manipulated predictive values of the cue (CP) are shown in Fig. 2 for the three groups.

To test if the experimental manipulation of CP affected the block-wise VEs (i.e., if participants indeed inferred the different cue-target contingencies), a 2 (*hemifield*: left/right) × 3 (*CP*: .8/.6/.4) × 3 (*group*: HC/LH/RH) ANOVA was performed. This ANOVA revealed significant main effects of *hemifield* [$F(1,77) = 7.88$; $p = .006$; $\eta_p^2 = .09$] and *CP* [$F(2, 154) = 22.54$; $p < .001$; $\eta_p^2 = .23$], as well as a significant interaction of both factors [$F(2, 154) = 10.98$; $p < .001$; $\eta_p^2 = .13$]. The main effect of group and interaction effects with the factor group were not significant. These results indicate that the experimentally manipulated predictive value of the cue modulated the validity effect in the expected way, with increased VEs with higher CP (see Fig. 2). The CP modulation was stronger for right than left targets, but VEs still increased with higher CP for left targets in HC and LH groups. Despite no significant interactions with the factor group, the expected linear pattern was visually not present for left targets in the RH group, in which the data also showed high interindividual variability (see Fig. 2, lower left plot).

This model-free analysis of average validity effects in each block shows that participants and patients were in principle able to infer the cue's predictive value on the basis of trial-wise observations. However, this model-free analysis can only be regarded as a proxy for this inference process, since the actual CP levels were unknown to the participants and because participants may potentially show considerable differences in this process (so that different trials have different

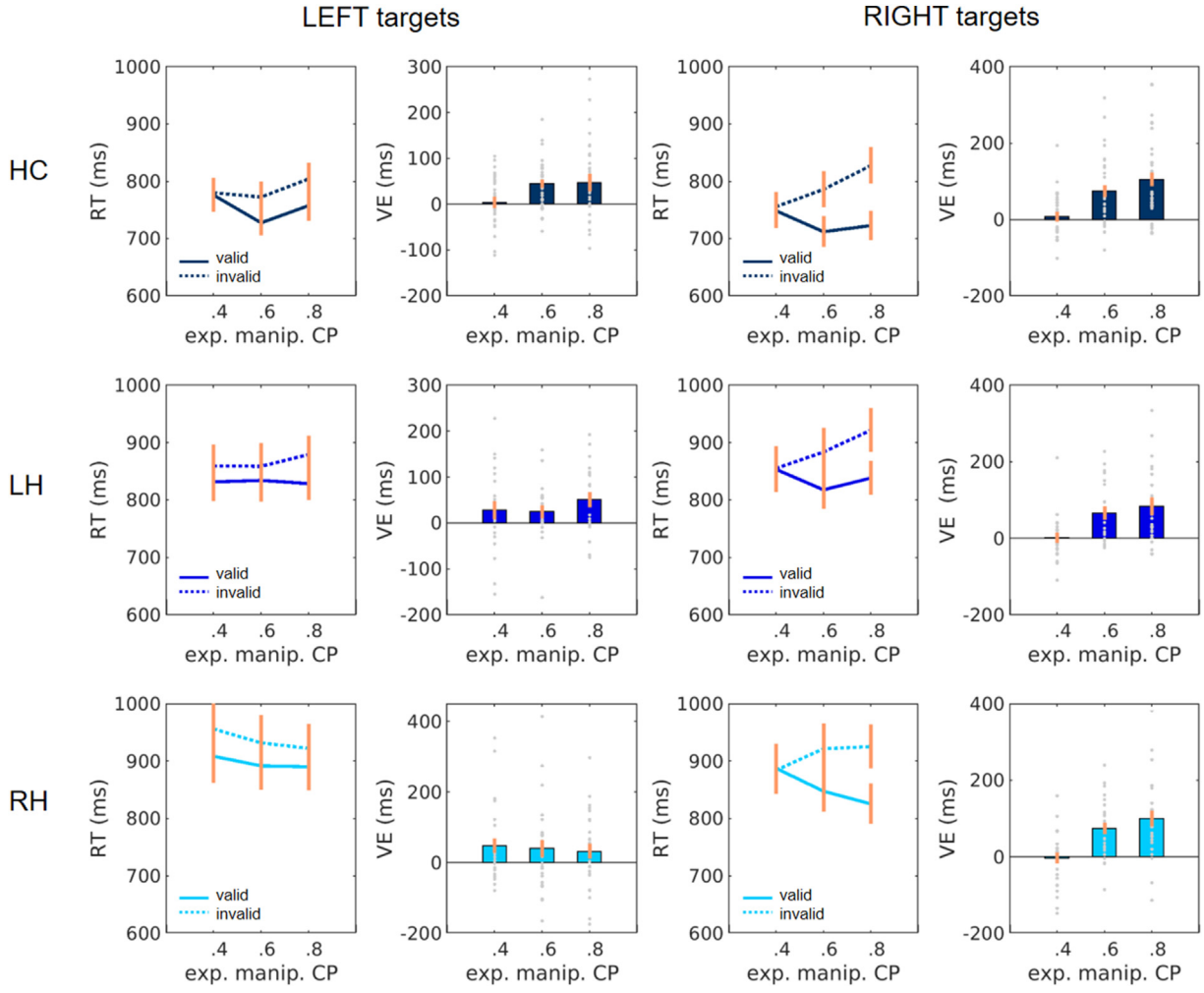

Fig. 2 – RTs for valid and invalid trials (line plots) and validity effects (VE = RT invalid minus RT valid, bar plots) as a function of the experimentally manipulated predictive value of the cue (CP) and target hemifield in each of the three groups. Error bars depict standard errors of the mean.

inferred predictive value for different participants). For this reason, we estimated participant-specific parameters of a formal RW-learning model in the next step, allowing for a more fine-grained assessment of the individual inference process and its effect on RTs.

3.4. Learning and response model parameters and their relation to neglect and lesioned hemisphere

Table 2 provides the mean learning and response model parameters. The 2 (*hemifield*: left/right) × 3 (*group*: HC/LH/RH) ANOVA on learning rates α revealed no significant effects. Similarly, the analysis of CP-sensitivity of RTs (ζ_2) with a 2 (*hemifield*: left/right) × 2 (*validity*: valid/invalid) × 3 (*group:* HC/LH/RH) ANOVA revealed no significant effects. None of these model parameters correlated with time post-stroke (all *p*-values >.3).

These results (again in line with the results from the model-free analyses) suggest that LH or RH damage is not per se related to aberrant inference of contingencies or the behavioral adaptation to these. These conclusions were also supported by Bayesian ANOVAs. These analyses yielded BF_{10}-values <.25 for models including main or interaction effects of the factor group. BF_{10}-values <.33 correspond to BF_{01}-values of >3, thereby providing moderate evidence for H_0 (Kelter, 2020).

Hence, the subsequent analyses investigated how altered learning and response model parameters may contribute to neuropsychological performance (as reflected in the four principal components of the current neuropsychological test battery) and how this depends on the lesioned hemisphere. Correlating the different Z-transformed α- and ζ_2-values with the component scores of PCA1 to PCA4 for all patients revealed one significant correlation between PCA1 and $Z\_\zeta_{2val\_ipsi}$ after Bonferroni-Holm correction ($r = -.64$; $p = 1 \times 10^{-6}$). Here, more substantial neglect symptoms (smaller PCA1 scores) were associated with a more pronounced modulation of RTs by the inferred predictive values of ipsilesional valid cues (higher $Z\_\zeta_{2val\_ipsi}$).

In the subsequent moderator analyses, the lesioned hemisphere was added as a dichotomous moderator of the relationship between the learning/response model parameter and neuropsychological performance (see Fig. 3A). Only one regression model was significant after Bonferroni-Holm correction. This model showed that the relationship between the first neglect component PCA1 and $Z\_\zeta_{2val\_ipsi}$ reported above was significantly moderated by the lesioned hemisphere [model summary: $R^2 = .51$; $F(3,41) = 15.42$; $p = 1e^{-6}$; X*W: R^2-change = .085; $F(1,42) = 7.28$; $p = .01$]. In other words, the correlation observed for the whole group was driven by the group of RH patients. As depicted in Fig. 3B, the hypersensitivity of RTs to the inferred predictive value of the cue (i.e., a high deviation of ζ_{2val_ipsi} from healthy controls) was associated with more severe neglect symptoms in RH (but not LH) patients. Hence, neglect symptoms in RH patients were related to an abnormally strong modulation by the inferred predictive values of ipsilesional cues (i.e., cues directing attention to the intact/non-neglected hemispace). In support of this, Bayesian linear regression comparing a model including the lesioned hemisphere × Z-scored model parameter interaction with a null model (including only the lesioned hemisphere and Z-scored model parameter) yielded a BF_{10} of 5.39 for $Z\_\zeta_{2val\_ipsi}$, i.e., moderate evidence (Kelter, 2020) for a moderator effect. The BF_{10} for the analyses with the learning rates amounted to .81 for Z_α_{contra} and .47 for Z_a_{ipsi}. Since these values are not <.33, they can only be regarded as anecdotal evidence against moderator effects for these parameters (Kelter, 2020).

To illustrate the effect of enhanced $Z\_\zeta_{2val\_ipsi}$ graphically, we split the RH group based on their scores on PCA1 and plotted moving averages across 6 trials of blockwise-normalized RTs against model-derived cue predictability scores (see Fig. 3C). This revealed a steeper decline in RTs to validly cued right targets in RH patients with negative scores for PCA1 (i.e., with more severe neglect symptoms). For completeness, we also compared the $Z\_\zeta_{2val\_ipsi}$ scores from six RH patients meeting cut-off scores for neglect on perceptual neglect tests (RH N+, cf. Supplementary Table S2) with the remaining RH N- patients and LH patients using non-parametric Mann-Whitney-U tests. Here, RH N+ patients showed significantly higher $Z\_\zeta_{2val\_ipsi}$ scores than LH patients ($p = .031$) and a trend towards higher $Z\_\zeta_{2val\_ipsi}$ scores than RH N- patients ($p = .062$), with no significant difference between LH and RH N- patients ($p = .696$).

For completeness, we also inspected the intercorrelation of the relevant model parameters across the RH patient group. This was done to see if the changes in model parameters for one hemifield were associated with changes in the other hemifield. This analysis revealed a positive correlation

Table 2 – Mean (±sd) of the model parameters for each group.

		Group		
		HC	LH	RH
Learning rates	α_L	.16 (±.11)	.20 (±.11)	.18 (±.11)
	a_R	.18 (±.11)	.21 (±.14)	.22 (±.13)
RT-level (intercept)	ζ_{1val_L}	662.90 (±111.42)	739.77 (±164.37)	816.25 (±219.71)
	ζ_{1val_R}	676.03 (±152.57)	767.92 (±142.66)	749.66 (±178.70)
	ζ_{1inval_L}	645.16 (±176.95)	757.30 (±154.43)	820.11 (±240.38)
	ζ_{1inval_R}	631.63 (±184.18)	750.50 (±181.16)	748.55 (±218.30)
CP-sensitivity of RTs	ζ_{2val_L}	199.72 (±174.23)	195.54 (±115.24)	194.28 (±140.22)
	ζ_{2val_R}	172.53 (±127.06)	166.89 (±99.80)	248.01 (±182.45)
	ζ_{2inval_L}	267.70 (±232.68)	184.11 (±128.74)	203.04 (±184.49)
	ζ_{2inval_R}	247.86 (±172.70	196.62 (±128.91)	248.44 (±161.55)

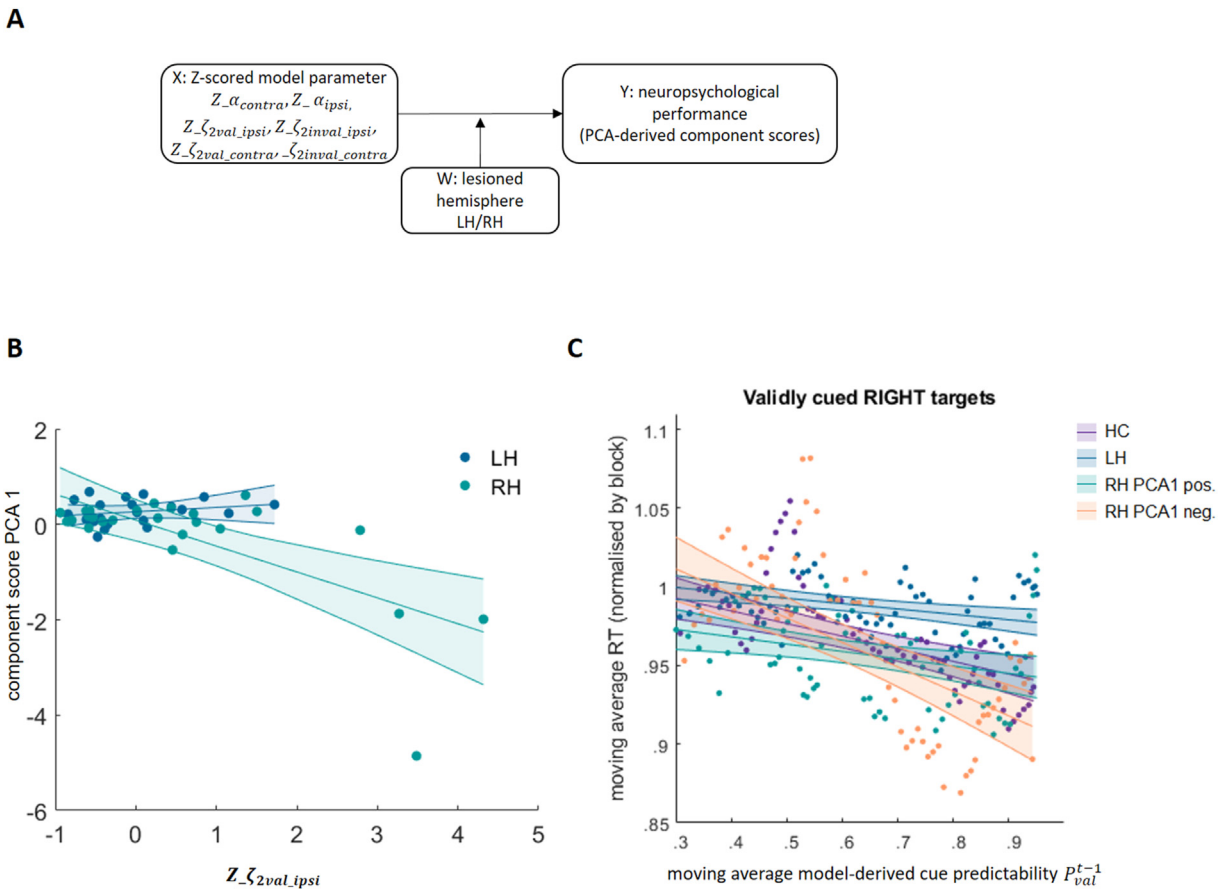

Fig. 3 – A) Procedure for the moderator analyses testing for hemisphere-specific associations between neuropsychological performance and abnormalities in the different model parameters: the relevant Z-transformed model parameter for prediction updating (Z_α) and RT sensitivity to predictions (Z_ζ_2) entered separate moderator analyses as predictors of neuropsychological test performance, using lesioned hemisphere as moderator. B) The main result of the significant moderator analysis showed that higher RT sensitivity to the inferred predictive value of the cue (Z-scored ζ_2-parameter) for ipsilesional valid cues were related to stronger impairment in the neglect tests contributing to PCA1. C) Illustration of effect of increased RT sensitivity to prediction to validly cued ipsilesional targets in HC, LH patients, and RH patients with mean Z-scores for PCA1 ≥0 and <0, respectively. RH patients with mean Z-scores <0 show the steepest decline in RTs with increasing model-derived probability that the cue will be valid/decreasing probability that the cue will be invalid.

between both learning rate parameters (Z_α_{contra} and Z_α_{ipsi}, $r = .51$, $p = .008$). Moreover, Z_ζ_{2val_ipsi} values were negatively correlated with Z_ζ_{2val_contra} values ($r = -.46$, $p = .019$). Hence, patients with a stronger modulation of RTs by predictive value for ipsilesional cues showed a weaker modulation for contralesional valid cues.

A plot of observed RT versus predicted (simulated) RT patterns for different model-derived CP bins is provided in Supplementary Figure S2. A model comparison between two reduced model versions, allowing either for hemifield-specific differences in learning rates α but not in RT sensitivity to inferred predictive value of the cue ζ_{2val} and ζ_{2inval} and vice versa, revealed that the model with the hemifield-specific ζ_2-parameters was superior to the model with hemifield-specific learning rates α [protected exceedance probability (PXP, Rigoux et al., 2014) for all participants: 1.0; for HC: .999, for LH: .942, for RH: .998]. Comparing the original model with hemifield-specific learning rates and hemifield- and validity-specific RT sensitivity to competing models with hemifield- and validity-specific learning rates (with or without hemifield-specific RT sensitivity) showed that the original model was superior to these models (PXP all participants .999; for HC: .653, for LH: .758, RH: .992). This finding suggests that allowing for variations of the learning rate according to validity besides or instead of the validity-related variation of RT sensitivity did not provide a better data model.

3.5. *Explicit evaluation of the cue's predictive value*

The mean discrepancy between the experimentally manipulated and the explicit rating of the cue's predictive value amounted to 10.20% (±5.06), 11.91% (±6.80), and 16.41% (±7.60) in the HC, LH, and RH groups, respectively. The one-way ANOVA revealed significant differences between the three groups [$F(2,77) = 6.97$; $p = .002$; $\eta_p^2 = .153$]. The post-hoc Tuckey-HSD test showed that the discrepancies were significantly higher for RH patients than for HC ($p = .001$) and by trend for LH patients ($p = .05$), with no significant differences

between LH patients and controls ($p = .611$). There were no significant correlations between Z-transformed discrepancy scores and any of the four neuropsychological PCA components after the Bonferroni-Holm correction. The moderator analyses did not yield any significant effects.

3.6. Summary of behavioral results

Taken together, the analyses of RTs (validity effects) and modeling parameters reflecting updating of the cue's predictive value and the sensitivity of RTs to inferred predictive value did not reveal any general impairments in RH or LH patients. Neglect test performance was not associated with altered learning rates but with a hypersensitivity of RTs to the predictive value of cues pointing validly towards ipsilesional space. A different picture emerged from the analysis of explicit measures of predictive processing, which were less precise in RH patients. Discrepancy scores were not significantly related to neuropsychological performance.

3.7. Lesion and disconnection symptom mapping

Fig. 4A and B show the overlap of the direct structural lesions and the disconnection maps derived from the HCP dataset. None of the lesion-symptom mapping (LSM) analyses revealed significant results at a cluster-corrected level. For the disconnection-symptom mapping (DSM) analyses, the only significant results were observed for RT hypersensitivity $Z\_\zeta_{2val\_ipsi}$ (see Fig. 4C and D). The analyses with all (LH and RH) patients yielded similar results (see Supplementary Figure S3), whereas no significant effects were observed when only LH patients were analyzed.

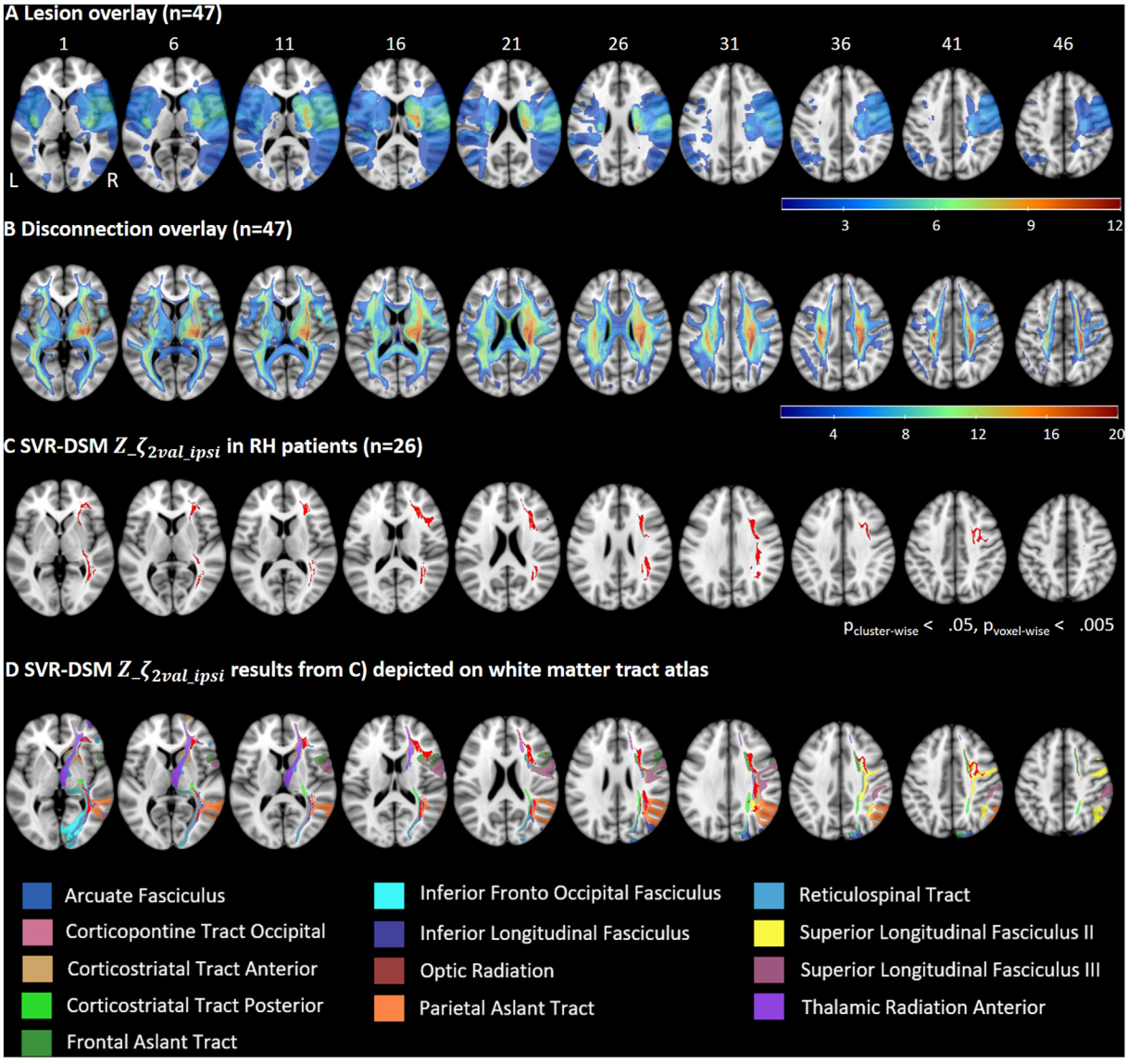

Fig. 4 – A) and B) The lesion and disconnection map overlays from $n = 47$ patients. C) Results of the support vector regression disconnection symptom mapping (SVR-DSM) in RH patients, showing disconnected areas associated with increased Z-scores for RT sensitivity to inferred cue predictability for ipsilesional valid trials. D) Overlay of the SVR-DSM results onto overlapping probabilistic tract maps from the Human Connectome Project (thresholded at 50% probability).

Table 3 – Number of suprathreshold voxels of the SVR-DSM results within the >50% probability maps of the HCP tracts. Only intersections of >50 voxels are reported. Results from the SVR-DSM with PCA1 scores are depicted for comparison.

Tract HCP atlas	number of suprathreshold voxels	
	$Z\_\zeta_{2val\_ipsi}$	PCA1-score
Inferior fronto-occipital fasciculus R	2422	–
Inferior longitudinal fasciculus R	1373	–
Superior longitudinal fasciculus II R	1139	1992
Arcuate fasciculus R	852	89
Parietal aslant tract R	814	138
Corticostriatal tract anterior R	716	–
Corticostriatal tract posterior R	671	9
Frontal aslant tract R	523	244
Thalamic radiation anterior R	458	–
Reticulospinal tract R	386	–
Superior longitudinal fasciculus III R	349	1600
Uncinate fasciculus R	177	–
Optic radiation R	106	–
Corticopontine tract occipital R	86	–

Table 3 lists the number of voxels from the DSM with $Z\_\zeta_{2val\_ipsi}$ within tracts from the HCP atlas (thresholded at 50% probability). Increased scores were related to disconnection within tracts connecting occipital and parietal regions to frontal areas (Inferior Fronto Occipital Fasciculus, Inferior Longitudinal Fasciculus, Superior Longitudinal Fasciculus II and III, Arcuate Fasciculus) as well as within temporo-parietal tracts (Parietal Aslant Tract).

No significant results were obtained when the severity of neglect symptoms (PCA1 scores) was regressed out of the $Z\_\zeta_{2val\_ipsi}$ scores, highlighting again the robust link between both measures. Still, an SVR-DSM analysis with the PCA1 neglect scores yielded results that overlapped only partially with those for $Z\_\zeta_{2val\_ipsi}$ and showed a higher overlap with the Superior Longitudinal Fasciculi II and III (see Table 3).

4. Discussion

This study employed a modified version of a Posner-type cueing paradigm with unsignaled changes in the cue's predictive value to investigate prediction-dependent spatial attention after stroke. Similar versions of this paradigm have been used in neuroimaging and neurostimulation studies in healthy participants. These studies revealed that neural activity in rTPJ covaries with the model-derived estimate of the cue's predictive value (Kuhns et al., 2017; Vossel et al., 2015) and that interference with rTPJ activity through TMS reduces the learning of the actual predictive value (Mengotti et al., 2017). The present study did not reveal any general impairments in prediction-dependent attention in LH or RH patients. However, RH patients exhibited a lower precision in explicitly rating the probability of valid cues in the different blocks. RTs were significantly modulated by the experimentally manipulated levels of the cue's predictive value so that the validity effect increased with a higher probability that the cue would be valid. The application of a Rescorla Wagner learning model neither revealed a significant difference in learning rates between the different groups nor significant correlations of learning rates with neglect symptoms. Moreover, RTs mostly followed the predictions from the computational model for left and right targets in all groups (see Supplementary Figure S2). However, neglect symptoms were significantly related to an abnormally strong modulation of RTs for ipsilesional validly cued targets in RH patients. This behavior was related to disconnection within temporo-parietal, fronto-parietal, and fronto-occipital white matter tracts. These findings speak against a generic updating deficit in patients with neglect. Instead, the prediction hypersensitivity suggests that neglect is related to abnormal predictive regulation of responses to ipsilesional events, implying that targeting this "hyperactive" ipsilesional processing may be beneficial in treating neglect patients.

The patient-specific neuropsychological profiles were derived from a PCA of the different tests. Although the sample size was at the lower end for this analysis, tests of different symptoms or syndromes mostly loaded on separate components as in previous studies with larger sample sizes (e.g., Latarnik et al., 2022). An exception was the star cancellation test, which generally showed a low sensitivity in the present patient sample. Previous work has not investigated the association between response bias and apraxia, and the present finding of a common component could reflect shared higher cognitive-motor control processes.

At first glance, the present findings seem at odds with the findings from healthy volunteers, according to which rTPJ is causally involved in the predictive inference of volatile cue-target contingencies in spatial cueing tasks (see, e.g., Mengotti, Käsbauer, et al., 2020, for a review). Neglect symptoms, commonly related to dysfunction of the fronto-parietal attention networks, including rTPJ, were not associated with decreased learning rates. This missing effect was substantiated by Bayesian model comparisons, which showed that a model with hemifield-specific differences in response model parameters was superior to models with hemifield-specific differences in learning rates. Moreover, inspection of the posterior correlations of learning rate and ζ_2-values showed that our model could identify the two parameters independently. One potential reason for the absence of learning rate differences could have been that only a few patients had direct structural lesions to the rTPJ region (cf. Fig. 4A). However, the number of patients with disconnection of temporo-parietal regions was considerably higher (cf. Fig. 4B), and the significant disconnection mapping results for RT sensitivity to predictions suggested that there was no general lack of power to detect effects. It should be noted that the effect of rTPJ neurostimulation on the learning rate in healthy participants was observed when applying online TMS, i.e., when rTPJ activity was not globally impaired but only transiently interrupted in a specific time window from 300 to 500 msec after target appearance (Mengotti et al., 2017). When rTPJ was disrupted for a more extended time through offline continuous theta burst stimulation (cTBS) in a subsequent study, the effects on the learning rate were less clear and depended on interindividual factors (such as performance in the sham session, as well as activity and connectivity of the right

anterior insula; Mengotti et al., 2022). Hence, there may be other determinants of predictive inference that become evident when rTPJ function is more severely compromised, i.e., after virtual and stroke-induced lesion/disconnection.

Moreover, it is currently poorly understood how prediction/prediction error signals from rTPJ are forwarded to other brain regions that eventually trigger behavioral responses. Work that incorporated behavioral responses into network modeling of fMRI data in a spatial cueing task suggested the intraparietal sulcus (IPS)'s crucial role in mapping network activity to behavioral output (Steinkamp et al., 2022). In the current study, disconnection of white matter tracts that may (amongst others) lead to disconnection of rTPJ was related to prediction hypersensitivity of RTs in ipsilesional space. This result could reflect an abnormal propagation of rTPJ signals to other areas, such as the IPS or frontal regions, which are involved in the context- (i.e., prediction-)sensitive regulation of behavior. Interestingly, a psychopharmacological study employing a serial probabilistic RT task revealed differential neurochemical correlates of learning and response adaptation (Marshall et al., 2016). Whereas an acetylcholine antagonist slowed the learning about stimulus transition contingencies, a dopamine antagonist modulated the sensitivity of RTs to model-derived volatility estimates with no effect on learning. Hence, the present study further corroborates this distinction between the neural mechanisms supporting the generation of predictions via learning and the adaptation of behavior to these predictions.

Besides the disconnection in posterior white matter regions, the present results pointed to a potential role of frontal pathways such as the frontal aslant tract and the anterior corticostriatal tract for prediction-dependent regulation of behavior. Interestingly, the frontal aslant tract has been implicated in the interaction between predictive and reactive response strategies by mediating the inhibition between the superior and inferior frontal gyrus (Tagliaferri et al., 2023). Moreover, frontostriatal tracts are crucial for different facets of response control (Haber, 2016), and one could speculate that these pathways are also involved in prediction-related selection and planning of responses.

The finding that neglect patients can still be sensitive to the probabilistic structure of tasks and cue predictability manipulations is in line with other studies. For instance, neglect patients showed response facilitation (faster RTs) when the probability for left targets was increased (Geng & Behrmann, 2002) and can use predictive spatial cues to improve their performance (Bartolomeo et al., 2001; Wansard et al., 2015). Still, this facilitation does not eliminate the neglect-specific spatial bias (Siéroff et al., 2007) and may be smaller than in healthy participants. Similar results have been observed in a study by Shaqiri and Anderson (2012), where stimuli appeared with 75% probability in a left "hotspot"-region, with 12.5% in a right "warm spot" on the opposite side, and with 12.5% probability in the remaining parts of the screen. Although RTs of neglect patients were generally slower for the contralesional hotspot than for the ipsilesional warm spot stimuli, RTs in the hotspot area were faster than in the remaining (less likely) contralesional locations. Hence, these studies provided evidence for (at least partially) preserved capabilities of neglect patients to infer the probability of sensory events and to regulate their behavior accordingly. However, studies focusing on the amplitude of electrophysiological (ERP) responses have reported marked deficits in probability-dependent processing in neglect (Dietz et al., 2021; Doricchi et al., 2021; Lasaponara et al., 2018). A study by Doricchi et al. (2021) was the first to exhibit that the pattern of abnormal brain responses in neglect patients differs for different levels within a processing hierarchy, as reflected in pre-attentive MMN and P300 responses to auditory stimuli. Since the patients in this task were only required to listen to the tone sequences passively, it remains to be investigated – just as for rTPJ responses (cf. above)–how and under which circumstances (e.g., task demands) these brain signals lead to differences in overt behavior. Still, it seems plausible that such altered neural signals observed in a passive task may underlie the hypersensitivity found in our active task.

Our study also revealed that the type of behavioral read-out may be another critical factor to consider in studies on prediction-dependent processing in stroke patients, and that different read-outs may contribute to discrepancies between different studies. In particular, we observed dissociations between the implicit (RT-based) measures and the explicit probability ratings of the patients. Similarly, findings from an auditory statistical learning paradigm in healthy volunteers demonstrated that RT-based and ERP(P300)-based measures do not correlate with explicit recognition measures (Batterink et al., 2015). In the present task, the overall discrepancy between the actual and rated block-specific predictive value of the cue was particularly enhanced in RH patients, and this effect was observed irrespective of the presence of neglect symptoms. This finding bears similarity to the results by Danckert et al. (2012), according to which RH patients with and without neglect had difficulties adapting their explicit choices to changes in the strategy of the computer opponent. Hence, one could speculate that RH damage may lead to problems developing explicit representations of probabilistic associations.

Interestingly, the ERP studies (Doricchi et al., 2021; Lasaponara et al., 2018) mentioned above demonstrated altered brain responses to contralesional and ipsilesional stimuli, as well as a "push–pull"-pattern of decreased contralesional and exaggerated ipsilesional processing. In the present study, neglect symptoms were also related to abnormal processing of predictions in ipsilesional space, and this ipsilesional RT *hyper*sensitivity was associated with a contralesional *hypo*sensitivity of RTs (as reflected in a significantly negative correlation of the two response model parameters). This is in line with other reports of aberrant cognitive processing in ipsilesional space in patients with neglect. For instance, Snow and Mattingley (2006) demonstrated that neglect patients are deficient in selecting relevant from irrelevant stimuli, as reflected in flanker distraction effects for task-irrelevant features of stimuli in ipsilesional space. Lasaponara et al. (2020) observed a significant association between line bisection performance and the CNV amplitude evoked by ipsilesional cues, highlighting that exaggerated ipsilesional processing is not limited to perceptual-attentional functions but also affects the preparation of motor responses. This finding converges with the observation of hyperexcitable parietal-motor pathways in the

intact left hemisphere of neglect patients (Koch et al., 2008). Hence, although the present results are in line with these reports, and with the finding of an attentional bias to contralesional objects (Rastelli et al., 2008), they significantly extent previous work by showing an over-adaption to predictions, rather than altered updating of predictions. It has been proposed that tasks requiring an adaptation to biased probabilities in left versus rights space may be an effective treatment strategy for neglect (Shaqiri et al., 2013), and the current findings support this notion by additionally emphasizing that improving inhibitory processing of highly probable stimuli in ipsilesional space may be beneficial to increase processing resources in the contralesional space.

One major limitation of the present work was the requirement to perform complex computerized tasks, which precluded the participation of patients with severe neglect. Therefore, neglect symptoms were mainly mild or potentially residual, and only present in a subset of patients when cut-off scores were applied in the present study. Still, our group of RH patients showed significantly slower RTs to contralesional targets and a stronger ipsilesional deviation in the Landmark-M task (PB-score) than LH patients. Although the task was already easier than the task in healthy controls (Kuhns et al., 2017; Mengotti et al., 2017, 2022), future studies should develop even simpler paradigms to assess prediction-dependent attention in severely affected patients to facilitate the investigation of larger patient samples with more severe neglect. This would be particularly important for the validation of the present lesion- and disconnection symptom mapping analyses, which need to be treated with caution due to the small sample size. In particular, due to the low number of patients with direct lesions of rTPJ, more work is needed to disentangle the role of direct rTPJ damage versus rTPJ disconnection. Moreover, the present patient sample was heterogeneous concerning the time post-stroke, precluding conclusions about the progression of the observed alterations and their relevance for recovery. As a further limitation, valid eye tracking data was unavailable in the present study, so the contribution of overt versus covert attentional processes remains unclear.

Despite these caveats, our findings provide important novel insights into the cognitive mechanisms underlying neglect-like symptoms by demonstrating an aberrant regulation of behavioral responses by predictions in ipsilesional space with preserved inference of probabilistic cue-target associations in a modified location-cueing task.

Scientific transparency statement

DATA: No raw or processed data supporting this research are publicly available.
CODE: All analysis code supporting this research is publicly available: https://osf.io/tupxk/.
MATERIALS: Some study materials supporting this research are publicly available, while some are subject to restrictions: https://osf.io/tupxk/.
DESIGN: This article reports, for all studies, how the author(s) determined all sample sizes, all data exclusions, all data inclusion and exclusion criteria, and whether inclusion and exclusion criteria were established prior to data analysis.
PRE-REGISTRATION: No part of the study procedures was pre-registered in a time-stamped, institutional registry prior to the research being conducted. No part of the analysis plans was pre-registered in a time-stamped, institutional registry prior to the research being conducted.
For full details, see the *Scientific Transparency Report* in the online version of this article.

CRediT authorship contribution statement

Simone Vossel: Writing – original draft, Supervision, Project administration, Methodology, Funding acquisition, Formal analysis, Conceptualization. **Anne-Sophie Käsbauer:** Writing – review & editing, Project administration, Investigation, Formal analysis, Conceptualization. **Paola Mengotti:** Writing – review & editing, Conceptualization. **Claudia C. Schmidt:** Writing – review & editing, Methodology. **Jochen Saliger:** Writing – review & editing, Resources, Conceptualization. **Hans Karbe:** Writing – review & editing, Resources, Conceptualization. **Gereon R. Fink:** Writing – review & editing, Resources, Funding acquisition, Conceptualization.

Data statement

The data are not publicly available, since the participants did not provide consent to public archiving. The digital anonymized raw data and the data underlying the tables and figures are archived in an institutional repository. Readers seeking access to the data should contact the lead author SV. Access to the repository will be granted to named individuals for scientific purposes in accordance with ethical procedures governing the reuse of the data. The raw clinical imaging data and reports cannot be shared, since they contain information that compromise the privacy of participants and are subject to confidentiality. Stimulus presentation, analysis and customized modelling code is openly available on the Open Science Framework at https://osf.io/tupxk/ (DOI: 10.17605/OSF.IO/TUPXK).

Conflict of interest

None.

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Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cortex.2024.12.007.

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