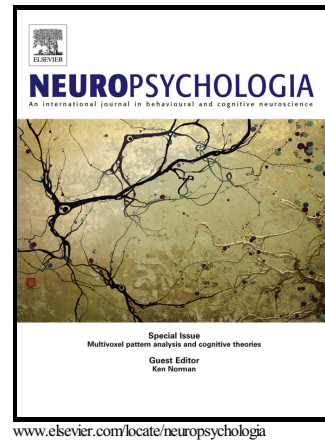


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Early sensory processing in right hemispheric stroke patients with and without extinction

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Abstract

While extinction is most commonly viewed as an attentional disorder and not as a consequence of a failure to process contralesional sensory information, it has been speculated that early sensory processing of contralesional targets in extinction patients might not be fully normal. We used a masked visuo-motor response priming paradigm to study the influence of both contralesional and ipsilesional peripheral subliminal prime stimuli on central target performance, allowing us to compare the strength of the early sensory processing associated with these prime stimuli between right brain damaged patients with and without extinction as well as healthy elderly subjects. We found that the effect of an informative subliminal prime in the left contralesional visual field on central target performance was significantly reduced in both right brain damaged patients with and without extinction. The results suggest that a

low-level early sensory deterioration of the neural representation for contralesional prime stimuli is a general consequence of right hemispheric brain damage unrelated to the presence or absence of extinction. This suggests that the presence of a spatial bias against contralesional information is not sufficient to elicit extinction. For extinction to occur, this spatial bias might need to be accompanied by a pathological (non-directional) reduction of attentional capacity.

Keywords

Extinction; Spatial Attention; Subliminal Perception; Right Hemisphere; Stroke

1 Introduction

The ability to perceive multiple simultaneously presented sources of visual information is a fundamental requirement allowing us to interact coherently with a complex visual environment. The importance of this ability is demonstrated by neurological patients suffering from extinction after unilateral, most commonly right hemispheric brain damage (Becker & Karnath, 2007). Extinction patients are not able to perceive targets presented on their contralesional left side in situations where these are presented together with targets presented on their ipsilesional right side. This disorder is most commonly viewed as an attentional disorder, namely as a consequence of biased competitive interactions between the ipsilesional and contralesional target representations. Specifically, it has been suggested that extinction might represent an exaggeration of the difficulty that healthy individuals have when required to attend and respond to multiple simultaneously presented targets (Duncan, Humphreys, & Ward, 1997; Duncan, 1998; Desimone & Duncan, 1995; Driver, Mattingley, Rorden, & Davis, 1997), possibly in combination with a pathological reduction of attentional capacity (de Haan, Karnath, & Driver, 2012; Driver et al., 1997; Karnath, 1988).

Despite the fact that extinction is usually not attributed to a complete failure of primary sensory processing (Driver & Vuilleumier, 2001), it has nevertheless been suggested that, compared to sensory processing in neurologically healthy subjects, sensory processing of contralesional targets in extinction patients might not be fully normal. Specifically, behavioural studies have suggested that in extinction patients a more subtle degradation of contralesional stimuli might already be present in unilateral situations where only a single stimulus is presented (Habekost & Rostrup, 2006; Schwartz, Marchok, Kreinick, & Flynn,

1979; Smania et al., 1998). While impaired processing of single contralesional stimuli can also occur in the absence of extinction (Habekost & Rostrup, 2006; Smania et al., 1998), the severity of this impairment has been shown to correlate with the severity of extinction (Habekost & Rostrup, 2006; Marzi et al., 1996; Schwartz et al., 1979). However, these studies all measured contralesional stimulus processing at the final processing stage of overt response. Electrophysiological studies suggest that the presentation of a visual target initially elicits a fast feedforward sweep where neural activation rapidly spreads from low-level areas to high-level areas. This initial feedforward sweep supports early sensory processing but not attention and subsequent overt report. To support attention and subsequent overt report, this fast feedforward sweep must be followed by subsequent recurrent processing where information from high-level areas is fed back to low-level areas via feedback connections (see Lamme & Roelfsema, 2000 for a review). Thus, overt responses to targets most likely reflect a range of processes including early sensory processes (initial feedforward processing), but also subsequent top-down effects from attentional processes (subsequent recurrent processing). As a consequence, effects seen at the level of overt response do not necessarily solely speak to the quality of primary sensory processing.

Potentially more informative in this light are neuroimaging studies that suggest that processing of single contralesional targets might already be impaired at an early sensory stage in extinction patients. Deouell, Bentin & Soroker (2000) presented right brain damaged patients suffering from auditory extinction with a train of auditory stimuli that were all identical on a certain stimulus dimension to either the left or the right ear. Infrequently, they presented an auditory stimulus differing on this dimension which normally elicits a so-called mismatch negativity in the ERP signal. This mismatch negativity is automatically elicited when the auditory input does not match the sensory predictions derived from preceding auditory inputs and is generally assumed to reflect early sensory processing (see Näätänen, Kujala, & Winkler, 2011 for a recent review). Deouell et al. (2000) found that the mismatch negativity evoked by deviant stimuli presented to the contralesional left ear was reduced both when compared to the mismatch negativity evoked by deviant stimuli presented to the ipsilesional right ear and when compared to the mismatch negativity evoked by deviant stimuli presented to the left ear in neurologically healthy elderly control subjects. These results suggest that early sensory processing of single contralesional stimuli is impaired in extinction patients. This is also supported by the results of a study performed by Eimer et al. (2002) who found that early somatosensory evoked potentials elicited by unilateral tactile

stimuli were reduced for contralesional tactile stimuli compared to ipsilesional tactile stimuli in a single patient suffering from tactile extinction, but not in two age-matched healthy subjects. However, as these studies by Deouell et al. (2000) and Eimer et al. (2002) did not assess brain damaged patients without extinction, it is currently unclear whether these results suggesting that, compared to early sensory processing in neurologically healthy subjects, early contralesional sensory processing is impaired in extinction patients, are truly specific to extinction patients or instead a general consequence of right hemispheric brain damage. Resolving this issue is highly relevant to current theories that aim to explain extinction. If early sensory deficits can be found in right brain damaged patients regardless of the presence of extinction, then these early sensory deficits are more likely to represent an epiphenomenon of the right hemispheric brain damage unrelated to extinction.

Thus, in the current study we aim to compare early sensory processing between brain damaged patients with extinction, brain damaged patients without extinction and neurologically healthy elderly subjects. We employ a masked visuo-motor response priming paradigm where a peripherally presented prime stimulus is rendered subliminal due to the subsequent presentation of a peripheral mask stimulus together with a centrally presented target stimulus that requires a two-alternative forced choice response. Specifically, we will vary the relationship between the prime and the target stimulus, so that the prime can either map onto the same response as the target (congruent), map onto the opposite response as the target (incongruent) or not map onto any response at all (neutral). Typically, when prime and target are presented in quick succession, this will result in a so-called positive compatibility effect (Schlaghecken & Eimer, 2000) with slower responses for incongruently primed targets and faster responses for congruently primed targets. Critically, behavioural, EEG and fMRI results suggest that this positive compatibility effect reflects early sensory processing, rather than e.g. attentional processing. Firstly, behavioural results from Schlaghecken & Eimer (2000) suggest that the positive compatibility effect is still present when attention is directed elsewhere by use of a cue and persists when primes are presented at unpredictable locations. Secondly, results from Eimer & Schlaghecken (1998) suggest that the positive compatibility effect is associated with an early direct visuo-motor activation of the correct response as indicated by an early lateralized readiness potential waveform in the ERP. Thirdly, fMRI results suggest that the neural correlate of this early direct visuo-motor activation of the correct response underlying the positive compatibility effect might be located in the primary motor cortex (unpublished data from Aron et al [2003] presented in Eimer & Schlaghecken

[2003]) or even brain structures operating functionally prior to this area (Schlaghecken, Münchau, Bloem, Rothwell & Eimer, 2003). Thus, studying the influence of both contralesional and ipsilesional subliminal prime stimuli on central target performance will allow us to assess the quality of the early sensory processing associated with these prime stimuli.

2 Methods and Materials

2.1 Participants

Over a 5-year period, all subsequently admitted patients suffering an acute first-ever right hemispheric stroke were screened at the Tübingen Center of Neurology for potential inclusion in the current study. This resulted in the detection of 17 patients suitable for inclusion (see Table 1 for patient characteristics). Inclusion criteria were: no evidence of older infarcts, no evidence of other neurological or psychiatric disorders, no evidence of non-correctable visual impairments (e.g. visual field defects, amblyopia, diplopia) and no spatial neglect. Visual field defects were assessed with the clinical confrontation technique, where the patient was required to detect a movement of the examiner's left or right index finger, presented in the patient's left or right visual field. Each patient was presented with 6 movements in each visual field, 2 in the upper quadrant, 2 on the horizontal meridian and 2 in the lower quadrant. The neglect assessment included the bells cancellation test, the letter cancellation test and the copying task (scored as described in Ferber & Karnath, 2001) and was performed to avoid confounding the potential effects of visual extinction on task performance with effects of spatial neglect. Additionally, 12 neurologically healthy elderly subjects (6 males, mean age 61 years old, range 50-74 years) participated in this study (control group). These control subjects all had no history of neurological or psychiatric disorders and presented with normal or corrected to normal vision. All participants were volunteers and gave their informed consent. The neurologically healthy elderly subjects were paid for participation in the study. The study was performed in accordance with the Declaration of Helsinki and approved by the ethics committee of the Medical Faculty of Tübingen (project number: 242/2008BO2).

2.2 Clinical assessment

Each neurological patient was clinically tested for visual extinction with a variation of the clinical confrontation technique where the patient was required to detect a movement of the examiner's left and/or right index finger presented in the patient's left and right visual field (see Table 1 for individual patient's performance). Each patient was presented with 10 unilateral left, 10 unilateral right and 10 bilateral movements. Additionally, to more precisely assess extinction severity, neurological patients were tested for visual extinction with a computerized task with time-critical presentation (see Table 1 for individual patient's performance). Each trial started with a central black fixation cross ($0.4^\circ \times 0.4^\circ$ visual angle) presented for a duration of either 1000ms or 2500ms and patients were instructed to continuously fixate this fixation cross. This was followed by the presentation of a peripheral green target stimulus on the horizontal midline at an eccentricity of 4.5° visual angle for a duration of 142.9ms. These target stimuli were identical to the prime stimuli used in the main masked visuo-motor response priming experiment (see below) and consisted of either an arrow pointing downward, an arrow pointing upward or a neutral symbol. Moreover, target stimuli could be presented either unilaterally left, unilaterally right or bilaterally. Thus, there were 6 possible unilateral target stimuli: up left, up right, down left, down right, neutral left and neutral right and 5 possible bilateral target stimuli: neutral left + neutral right, up left + neutral right, neutral left + up right, down left + neutral right and neutral left + down right (see also Figure 2B). Patients were required to vocally report the location and orientation of the target(s) presented (i.e. 'left up' or 'right neutral and left down') while the experimenter logged these vocal responses with a keyboard. Finally, after the experimenter had made sure the patient was fixating the central fixation cross, the next trial was initiated by the experimenter with a keyboard response. In a single session, patients were presented with 12 unilateral left, 12 unilateral right and 40 bilateral targets with each of the possible target stimuli (6 unilateral and 5 bilateral) occurring equally often in pseudo-randomized order.

Patients were classified as showing visual extinction when they failed to report at least 50% of the contralesional movements during bilateral stimulation in the presence of correct detection of at least 90% of the contralesional movements during unilateral stimulation during the assessment with the clinical confrontation technique. The results of the computerized visual extinction task were comparable with the results from the assessment with the clinical confrontation technique: Patients demonstrating extinction during the assessment with the clinical confrontation technique also demonstrated extinction during the computerized visual extinction task and patients not demonstrating extinction during the

assessment with the clinical confrontation technique also did not demonstrate extinction during the computerized visual extinction task. However, the computerized visual extinction task also revealed that 2 patients (patients 313 and 314) failed to detect some of the contralesional stimuli, regardless of whether these stimuli were presented unilaterally or bilaterally (see Table 1). This suggests that these patients might have suffered from a general contralesional visual impairment. As in these patients, performance on our masked visuo-motor response priming paradigm with peripherally presented prime stimuli (see below) could not be safely interpreted, we excluded these 2 patients from all further analyses.

Thus, we divided the patients in 2 groups. The first group contained 5 patients with extinction (EXT group), the second group contained 10 patients without extinction (RBD group). Statistical comparisons using Mann-Whitney U tests revealed no significant differences in either contralesional (Letter: $p=.300$; Bells: $p>.999$) or ipsilesional (Letter: $p>.999$; Bells: $p=.396$) omissions during the neglect assessment between patients with and without extinction. Likewise, there was no evidence for a significant difference in age between either healthy control subjects and patients with extinction ($p = .663$), healthy control subjects and patients without extinction ($p > .999$) or patients with and patients without extinction ($p = .762$). Finally, we found no difference in time since stroke between patients with and patients without extinction ($p = .679$).

--- Insert Table 1 around here ---

2.3 Lesion mapping

For lesion mapping, we used the brain images collected as part of the routine clinical investigation after the patient was admitted to the Tübingen Center of Neurology due to acute onset of stroke symptoms. For each patient, we selected the image with the clearest demarcation of the lesion. Four patients were investigated with magnetic resonance (MR) imaging (2 in the EXT and 2 in the RBD group) and in these patients the lesion was most clearly demarcated in the diffusion-weighted images. These diffusion-weighted images covered the whole brain with an in-plane resolution of 0.9 x 0.9 mm and a slice thickness of 6 mm. The remaining 11 patients were investigated with spiral computed tomography (CT) with images covering the whole brain. Nine of these CT images had an in-plane resolution of 0.4 x 0.4 mm and a slice thickness varying between 4.5 and 4.8 mm, the remaining 2 images had an in-plane resolution of 0.5 x 0.5 mm and a slice thickness of 4.5 mm. The time between

stroke and collection of the images used for lesion mapping was on average 2.8 days for the EXT group and 3.0 days for the RBD group.

For each patient, the lesion was semi-automatically delineated with the Clusterize toolbox (de Haan et al., submitted: <http://www.medizin.uni-tuebingen.de/kinder/en/research/neuroimaging/software/>). Both the lesion map and the patient image were subsequently transferred into stereotaxic space using the Clinical toolbox (Rorden, Bonilha, Fridriksson, Bender & Karnath, 2012: <http://www.nitrc.org/plugins/mwiki/index.php/clinicaltbx:MainPage>), which includes a CT template for normalisation. For determination of the transformation parameters, cost-function masking was employed (Brett, Leff, Rorden & Ashburner, 2001). Both the Clusterize and the Clinical toolbox were used with SPM8, running under Matlab R2013b (The Mathworks, Inc., Natick, MA). Finally, the normalised lesion maps of the patients with and the patients without extinction were separately superimposed to create an overlap image for both the EXT and the RBD group. As can be seen from Figure 1, in both groups, lesion overlap was maximal in the striato-capsular region. Importantly, in both groups, damage to early sensory cortical areas was rare. This suggests that damage to early sensory cortical areas cannot explain the results obtained in our masked visuo-motor response priming experiment (see below).

--- Insert Figure 1 around here ---

2.4 Procedure

The software package MEL Professional (Psychological Software Tools Inc.) running under a DOS environment on a PC was used to present the stimuli. The monitor was a 16 inch cathode ray tube monitor with a refresh rate of 70Hz. Participants were seated in front of the computer screen at a distance of approximately 57cm. The background colour of the computer screen was always white.

In the main masked visuo-motor response priming experiment, each trial started with a central black fixation cross ($0.4^\circ \times 0.4^\circ$ visual angle) presented for a duration of either 1000ms or 2500ms and participants were instructed to continuously fixate this fixation cross (see Figure 2). This was followed by a 14.3ms presentation of a peripheral green prime stimulus (RGB 60,180,60; $3.3 \times 1.2^\circ$ visual angle) presented on the horizontal meridian at an eccentricity of 4.5° visual angle. Prime stimuli were adapted from Vorberg et al. (2003) and

could be informative or uninformative. Informative primes were either an arrow pointing up ('up') or an arrow pointing down ('down') and uninformative primes consisted of a neutral symbol ('neutral'). Moreover, the prime stimuli could be presented unilaterally left, unilaterally right or bilaterally, where bilateral primes consisted of either 2 uninformative primes or an informative and an uninformative prime (i.e. never 2 informative primes). Thus, there were 6 possible unilateral primes: up left, up right, down left, down right, neutral left and neutral right and 5 possible bilateral primes: neutral left + neutral right, up left + neutral right, neutral left + up right, down left + neutral right and neutral left + down right (see Figure 2B). Subsequently, following a prime-target onset asynchrony of 85.7ms, a central target and 2 peripheral metacontrast masks were presented for a duration of 142.9ms. The metacontrast masks ($5.4^\circ \times 1.8^\circ$ visual angle) appearing simultaneously with the central target were presented on the horizontal meridian at an eccentricity of 4.5° visual angle and were designed to prevent conscious awareness of the primes. The central target ($3.3^\circ \times 1.2^\circ$ visual angle) was either an arrow pointing up or an arrow pointing down. Combined, the prime and the target stimuli thus built one of 3 possible prime-target congruency conditions: congruent (informative prime and target arrow pointing in the same direction), incongruent (informative prime and target arrow pointing in the opposite direction) and neutral (uninformative prime(s) and a target arrow pointing up or down). Participants were instructed to identify the central target arrow and vocally report its orientation as 'up' or 'down' as fast and accurately as possible. The peripherally presented subliminal prime(s) and supraliminal masks were thus task-irrelevant and participants were told to simply ignore the peripheral stimuli. The reaction time of the start of the vocal response was automatically recorded with a throat microphone (Throat Mic Sportsman Edition, Firefox Technologies) and the participant's answer was logged by the experimenter with a keyboard.

--- Insert Figure 2 around here ---

Finally, after the experimenter had made sure the participant was fixating the central fixation cross, the next trial was initiated by the experimenter with a keyboard response. In each session, participants were presented with 10 repetitions of each trial type (unilateral congruent informative prime left, unilateral incongruent informative prime left, unilateral neutral prime left, unilateral congruent informative prime right, unilateral incongruent informative prime right, unilateral neutral prime right, bilateral congruent informative prime

left, bilateral incongruent informative prime left, bilateral congruent informative prime right, bilateral incongruent informative prime right, bilateral neutral prime), occurring in pseudo-randomized order. All participants completed at least 2 sessions (i.e. 20 repetitions per condition) with most participants completing 3 sessions (i.e. 30 repetitions per condition).

To assess whether participants might have consciously perceived the prime stimuli despite their short presentation duration and the metacontrast masking, a subset of the participants was presented with a control experiment. This experiment was a modified version of the masked visuo-motor response priming experiment. Participants were informed of the presence of the peripheral prime stimuli and were required to first report the identity of the central target and secondly to guess the identity of the prime stimuli. Moreover, primes were always unilateral (i.e. up left, up right, down left, down right, neutral left or neutral right). The participant's vocal responses were logged by the experimenter with a keyboard. In a single session, participants were presented with 10 repetitions of each trial type presented in pseudo-randomized order.

2.5 Analyses

For the masked visuo-motor response priming experiment, both reaction times and response accuracy of responses to the centrally presented targets were analysed in SPSS using a 3 (group: EXT, RBD or controls) by 2 (prime presentation condition: unilateral or bilateral) by 2 (informative prime location: left visual field [LVF] or right visual field [RVF]) by 3 (prime-target congruency: congruent, incongruent or neutral) mixed model ANOVA with subsequent post-hoc mixed-model ANOVAs, repeated measures ANOVAs, independent-samples t-tests and paired-samples t-tests when necessary. For the reaction time data, incorrect trials and trials where the reaction time either fell below 150ms or exceeded 1500ms were excluded from the analyses. This resulted in the exclusion of 3.93% of the trials in right brain damaged patients with extinction, 2.00% of the trials in right brain damaged patients without extinction and 1.06% of the trials in the neurologically healthy elderly subjects. Results of the control experiment were analysed in SPSS with a one-sample t-tests to determine whether guessing accuracy for primes presented in the left or right visual field was significantly better than chance (33.33%), which would suggest that the participants consciously perceived the primes. Additionally, we performed a paired-samples t-test to assess whether prime visibility different depending on whether the prime was presented in the left or the right visual field.

Mauchly's sphericity test was used to assess sphericity and a Greenhouse-Geisser correction was used whenever the assumption of sphericity was violated. Levene's test was used to assess homoscedasticity and the degrees of freedom were adjusted whenever the assumption of homoscedasticity was violated. Finally, the Shapiro-Wilk test was used to assess normality and non-parametric tests were used whenever the assumption of normality was violated. All p-values reported are Bonferroni corrected for multiple comparisons when appropriate. For all statistical tests, an alpha value of .05 was used.

3 Results

3.1 Control experiment

The results of the control experiment that aimed to assess visibility of the prime stimuli are presented in Figure 3. The control experiment was performed by 1 neurologically healthy subject, 2 right brain damaged patients with extinction and 6 right brain damaged patients without extinction. As can be seen from Figure 3 virtually all participants achieved close to perfect accuracy when required to identify the central target, while simultaneously demonstrating guessing rates that were close to chance for the peripheral prime stimuli (33.33%). The only exception was participant RBD203 who managed to accurately guess the identity of the prime stimuli in around 50% of the trials, however, at the detriment of performance accuracy in response to the central target. Critically, for this participant performance accuracy for the central target was considerably lower during the control experiment (86.7%) than during the main masked visuo-motor response priming experiment (99.4%). This suggests that this participant might have employed different strategies in the control and masked visuo-motor response priming experiments, allocating cognitive resources away from the central target to the peripheral prime stimuli in the control experiment, but not in the masked visuo-motor response priming experiment.

Subsequent one-sample t-tests on the guessing accuracy in response to the prime stimuli in either all 9 participants or the 8 neurological patients demonstrated that guessing rates were not significantly better than chance for either primes presented in the left visual field (all participants: $t_8=.987$, $p=.353$; neurological patients only: $t_7=1.333$, $p=.224$) or primes presented in the right visual field (all participants: $t_8=.859$, $p=.415$; neurological patients only: $t_7=.683$, $p=.516$), suggesting that the neurological patients did not consciously perceive the primes. Finally, a paired-samples t-test on the guessing accuracy in response to

the prime stimuli in either all 9 participants or the 8 neurological patients revealed no significant difference in guessing accuracy between primes presented in the left or the right visual field (all participants: $t_8=.409$, $p=.693$; neurological patients only: $t_7=0.945$, $p=.376$), suggesting that for neurological patients prime visibility did not differ between primes presented in the left visual field and primes presented in the right visual field and that differences in prime visibility thus cannot explain the results obtained in the masked visuo-motor response priming experiment (see below).

--- Insert Figure 3 around here ---

3.2 Masked visuo-motor response priming experiment: accuracy

Performance accuracies for the central target for each of the trial types in the masked visuo-motor response priming experiment are shown in Table 2. Critically, as can be seen from Table 2, performance accuracy for the central target was virtually perfect in all participant groups regardless of trial type. Accordingly, the 3 (group: EXT, RBD or controls) by 2 (prime presentation condition: unilateral or bilateral) by 2 (informative prime location: left visual field [LVF] or right visual field [RVF]) by 3 (prime-target congruency: congruent, incongruent or neutral) mixed model ANOVA on the performance accuracies to the central target revealed no significant main or interaction effects.

--- Insert Table 2 around here ---

3.3 Masked visuo-motor response priming experiment: reaction times

Reaction times to the central target for each of the trial types in the masked visuo-motor response priming experiment are shown in Figure 4. The 3 (group: EXT, RBD or controls) by 2 (prime presentation condition: unilateral or bilateral) by 2 (informative prime location: left visual field [LVF] or right visual field [RVF]) by 3 (prime-target congruency: congruent, incongruent or neutral) mixed model ANOVA on the reaction times to the central target revealed a significant main effect of group ($F_{2,24}=11.638$, $p<.001$), a significant main effect of prime-target congruency ($F_{1,604,38,487}=31.150$, $p<.001$), a significant interaction between prime-target congruency and group ($F_{3,207,38,487}=3.986$, $p=.013$) and a significant interaction between prime-target congruency and informative prime location ($F_{2,48}=16.626$, $p<.001$) that were however all qualified by a significant 3-way interaction between prime-target

congruency, informative prime location and group ($F_{4,48}=3.141$, $p=.023$). We performed post-hoc tests to determine the source of this 3-way interaction. We were predominantly interested in comparing the effect of prime-target congruency between the groups, and not in comparing the effect of prime-target congruency between the visual fields. Thus, we performed separate post-hoc mixed model ANOVAs with the factors group and prime-target congruency for each level of the factor informative prime location.

--- Insert Figure 4 around here ---

When the informative prime was presented in the right visual field, the post-hoc 3 (group) by 3 (prime-target congruency) mixed model ANOVAs on the reaction times to the central target showed a significant main effect of both group ($F_{2,24}=11.349$, $p<.001$) and prime-target congruency ($F_{2,48}=43.137$, $p<.001$), while the interaction between these factors failed to reach significance ($F_{4,48}=1.770$, $p=.300$), suggesting that when the informative prime was presented in the right visual field, the effect of prime-target congruency did not differ significantly between the different groups. Reaction times were overall higher in neurological patients than in healthy elderly subjects (EXT vs. controls: $t_{15}=3.511$, $p=.005$; RBD vs. controls: $t_{20}=4.367$, $p<.001$), but did not significantly differ between patients with extinction and patients without extinction (EXT vs. RBD: $t_{13}=.141$, $p>.999$). Moreover, over all groups reaction times were significantly faster when the informative prime and target were congruent ($t_{26}=2.354$, $p<.026$) and significantly slower when the informative prime and target were incongruent ($t_{26}=7.687$, $p<.001$) compared to when the informative prime and target were neutral.

More interestingly, when the informative prime was presented in the left visual field, the post-hoc 3 (group) by 3 (prime-target congruency) mixed model ANOVAs on the reaction times to the central target also showed a significant main effect of group ($F_{2,24}=11.815$, $p<.001$) and prime-target congruency ($F_{2,48}=8.691$, $p=.002$). However, these main effects were now qualified by a significant 2-way interaction ($F_{4,48}=6.195$, $p<.001$), suggesting that when the informative prime was presented in the left visual field, the effect of prime-target congruency on reaction times significantly differed between groups. To determine the groups between which the effect of prime-target congruency on reaction times in trials where the informative prime was presented in the left visual field was different, we

performed a 2 (group) by 3 (prime-target congruency) mixed model ANOVA for each possible combination of groups (i.e. EXT and controls, RBD and controls or EXT and RBD). These ANOVAs revealed that whereas the effect of prime-target congruency on reaction times differed significantly between neurological patients with extinction and healthy subjects ($F_{2,30}=10.764$, $p<.001$) and between neurological patients without extinction and healthy subjects ($F_{2,40}=7.992$, $p=.003$), it did not differ significantly between neurological patients with extinction and neurological patients without extinction ($F_{2,26}=1.350$, $p=.831$). Subsequent 1 by 3 (prime-target congruency) ANOVAs revealed that this was caused by the main effect of prime-target congruency in trials where the informative prime was presented in the left visual field reaching significance in healthy subjects ($F_{2,22}=39.343$, $p<.001$), with significantly faster reaction times in congruent trials ($t_{11}=3.519$, $p=.005$) and significantly slower reaction times in incongruent trials ($t_{11}=7.908$, $p<.001$) than in neutral trials, while this main effect of prime target congruency failed to reach significance in either neurological patients with ($F_{2,8}=2.145$, $p=.540$) or without ($F_{2,18}=.351$, $p>.999$) extinction. Thus, compared to neurologically healthy subjects, when the informative prime was presented in the left visual field, the effect of prime-target congruency was significantly reduced in both neurological patients with and neurological patients without extinction, while the effect of prime-target congruency did not differ significantly between the neurological patients with and neurological patients without extinction.

Previous research suggests that the effect of prime-target congruency on central target performance in our masked visuo-motor priming paradigm reflects early sensory processing, rather than attentional processing (see introduction). Nevertheless, it is theoretically possible that the reduced effect of prime-target congruency in trials where the informative prime was presented in the left, contralesional visual field (i.e. the contralesional prime-target congruency effect) in our neurological patients was caused by a (subclinical) attentional deficit. To address this issue directly, we additionally performed Pearson product-moment correlation analyses to test whether, over all neurological patients (i.e. both EXT and RBD), the magnitude of the contralesional prime-target congruency effect was correlated with the severity of the contralesional attentional deficit. We determined the magnitude of the contralesional prime-target congruency effect by subtracting the reaction times in trials where a congruent prime was presented in the left visual field from the reaction times in trials where an incongruent prime was presented in the left visual field. The severity of the contralesional attentional deficit was determined by either amount of contralesional omissions in the Bells

task, amount of contralesional omissions in the Letter task or the subtraction of the percentage of left-sided omissions during unilateral trials from the percentage of left-sided omissions during bilateral trials in the computerized extinction task. Our reasoning was that if the significant reduction of contralesional prime-target congruency effects in neurological patients could be attributed to attentional deficits, contralesional prime-target congruency effects should be smaller the larger the patient's contralesional attentional deficit, i.e. the magnitude of the contralesional prime-target congruency effect should be negatively correlated with the severity of the contralesional attentional deficit. Contrary to this prediction, however, the contralesional prime-target congruency effect was numerically positively correlated with the amount of contralesional omissions in the Letter cancellation task ($r_{15} = .155$, $p > .999$), the amount of contralesional omissions in the Bells cancellation task ($r_{15} = .593$, $p = .060$) and the amount of contralesional extinctions during bilateral trials in the computerised extinction task ($r_{13} = .061$, $p > .999$), with this positive correlation almost reaching significance for contralesional omissions in the Bells cancellation task. This demonstrates that, if anything, contralesional prime-target congruency effects tended to be larger in those patients with more severe attentional deficits instead of smaller. This suggests that the reduction of the contralesional prime-target congruency effect in our right brain damaged patients, when compared to the prime-target congruency effect in healthy controls, cannot be attributed to attentional deficits.

The original 3 (group: EXT, RBD or controls) by 2 (prime presentation condition: unilateral or bilateral) by 2 (informative prime location: left visual field [LVF] or right visual field [RVF]) by 3 (prime-target congruency: congruent, incongruent or neutral) mixed model ANOVA on the reaction times to the central target additionally also revealed a significant main effect of prime presentation condition ($F_{1,24}=25.140$, $p<.001$) with faster reaction times to central targets that were preceded by bilateral primes than central targets that were preceded by unilateral primes. As unilateral primes were effectively made bilateral by the addition of an uninformative neutral prime stimulus in the opposite visual field, this result suggests that adding an uninformative task-irrelevant subliminal prime to a prime display facilitated responses to the subsequently presented central target. This observation is in line with findings from neuroimaging studies that suggest neural activity in early visual areas increases as more stimuli are shown even if these are task-irrelevant and unattended (Schwartz et al., 2005; Todd & Marois, 2004).

4 Discussion

The aim of the study was to investigate whether the observation from previous studies that extinction patients demonstrate early sensory impairments in their contralesional hemifield (Deouell et al., 2000; Eimer et al., 2002) is truly specific to extinction patients or instead a general consequence of unilateral brain damage. We used a masked visuo-motor response priming paradigm to study the influence of both contralesional and ipsilesional peripheral subliminal prime stimuli on central target performance, allowing us to compare the strength of the early sensory processing associated with these prime stimuli between neurological patients with extinction, neurological patients without extinction and healthy elderly subjects (Eimer & Schlaghecken, 2003; Schlaghecken & Eimer, 2000). The effect of an informative subliminal prime in the right ipsilesional visual field on central target performance was present and comparable between the three groups. More interestingly however, the effect of an informative subliminal prime in the left contralesional visual field on central target performance was (compared to healthy elderly subjects) significantly reduced in both neurological patients with extinction and without extinction. Results from previous studies suggest that the prime-target congruency effects in our masked visuo-motor priming paradigm reflect early sensory processing rather than attentional processing (Eimer & Schlaghecken, 1998; 2003; Schlaghecken & Eimer, 2000; Schlaghecken et al., 2003). Our observation that the reduction of the effect of a contralesional informative subliminal prime on central target performance tended to be stronger in patients with weaker attentional deficits (neglect and extinction) than in patients with stronger attentional deficits, likewise suggests that these reduced effects of a contralesional informative subliminal prime on central target performance cannot be attributed to (subclinical) attentional deficits. These results suggest that contralesional early sensory processing is impaired in right brain damaged patients independently of the presence of extinction. In other words, our results suggest that early sensory deficits are an epiphenomenon of unilateral right hemispheric brain damage unrelated to extinction.

Our masked visuo-motor response priming paradigm is in some ways similar to Eriksen & Eriksen's (1974) flanker task. In the common version of this flanker task, subjects have to provide a two-alternative forced choice response to a central target while simultaneously irrelevant peripheral flankers are presented. Critically, these irrelevant peripheral flankers can be congruent with the central target (i.e. indicating the same response), incongruent with the central target (i.e. indicating opposite responses) or neutral

(not indicating either of the two possible responses). A typical finding in healthy subjects is that incongruent peripheral flankers negatively affect responses to the central target, whereas congruent peripheral flankers positively affect responses to the central target. There are two main differences between the flanker task and our masked visuo-motor response priming paradigm: Firstly, the peripheral flankers in the flanker task are supraliminally presented whereas primes were subliminally presented in our masked response priming paradigm. Secondly, the peripheral flankers in the flanker task are presented simultaneously with the central target whereas primes were presented ahead of the central target in our masked response priming paradigm. Nevertheless, this flanker task has repeatedly been used to demonstrate that irrelevant contralesional stimuli can influence central target performance in patients suffering from extinction and/or neglect (Audet, Bub & Lecours, 1991; Cohen, Ivry, Rafal & Kohn, 1995; Danckert, Maruff, Kinsella, de Graff & Currie, 1999; Danckert et al., 2000; Lavie & Robertson, 2001; Morein-Zamir, Henik, Balas & Soroker, 2005; Ro, Cohen, Ivry & Rafal, 1998; Snow & Mattingley, 2006, 2008). At first glance, our finding of a reduction of the effect of a contralesional prime on central target performance in neurological patients seems to contradict these observations made with the flanker task. However, a closer inspection of the results from these studies using the flanker task in patients suffering from extinction and/or neglect, reveals that the influence of contralesional flankers on central target performance is often (statistically and/or numerically) reduced compared to the influence of ipsilesional flankers on central target performance (Cohen et al., 1995; Lavie & Robertson, 2001; Morein-Zamir et al., 2005; Ro et al., 1998; Snow & Mattingley, 2006, 2008) and, though rarely assessed in the same study, the influence of left-sided flankers on central target performance in healthy subjects (Snow & Mattingley, 2006, 2008). Thus our finding of a reduction of the effect of a contralesional prime on central target performance in extinction patients, when compared to neurologically healthy subjects, is in line with previous results from studies that used the flanker task to assess implicit perception in the contralesional visual field. Importantly, the novel aspects of our study lie in the fact that the masked visuo-motor response priming paradigm allowed us to assess the quality of early sensory processing. Moreover, in contrast to the previous studies that used the flanker task in extinction/neglect patients, we additionally investigated right brain damaged patients without extinction. This allowed us to assess whether any early contralesional sensory deficits revealed by the masked visuo-motor response priming paradigm were specific to extinction patients or instead a more general consequence right brain damage. Consequently, we were

able to demonstrate that early contralesional sensory processing is reduced in right brain damaged patients independently of the presence of extinction.

One interesting question is why our right brain damaged patients displayed sensory deficits. While some of our patients did present with brain damage in early sensory cortical areas, most of our patients did not. Thus, our finding of an early sensory deficit in right brain damaged patients both with and without extinction cannot simply be explained by damage to early sensory areas in the brain. In light of several recent findings that suggest that focal brain lesions can result in widespread network dysfunction (e.g. Gratton, Nomura, Pérez & D'Esposito, 2012; Irimia & Van Horn, 2014), one possible reason why our patients demonstrated an early sensory deficit in absence of damage to early sensory areas might be that the focal lesions caused widespread functional impairments even in intact early sensory areas remote from the brain lesion.

Extinction is generally seen as a consequence of biased competitive interactions between target representations for access to limited resources, where unilateral brain damage weakens contralesional target representations, leaving them unable to successfully compete with the stronger ipsilesional target representations in competitive situations (Desimone & Duncan, 1995). A key feature of this view is that competitive interactions are integrated between areas in the sensorimotor network so that when a target representation loses the competition for access to limited resources in one area, it will also lose this competition in other areas throughout the entire network (Duncan 1998; Duncan, 2006; Duncan et al., 1997). Thus, regardless of where in the processing pipeline the contralesional target representation is weakened, the end result is invariably a global bias against that contralesional target, i.e. an early contralesional sensory deficit should invariably lead to a global spatial bias against contralesional targets and subsequent extinction. Our finding that contralesional early sensory deficits can occur independently of the presence of extinction then has two possible implications.

The first possible implication is that the proposal that competitive interactions are integrated between areas in the sensorimotor network is wrong and that early contralesional sensory deficits do not necessarily lead to a global bias against contralesional targets. Instead, to elicit a global bias against contralesional targets and subsequent extinction, the weakening of contralesional target representations might have to occur at a specific point in the processing pipeline and/or sensorimotor area. Evidence at the neural level, however, suggests the presence of a widespread maintenance of selected target representations paired with a

widespread suppression of non-selected target representations in the sensorimotor network and thus tends to support the idea that competitive interactions are integrated between areas in the sensorimotor network (see Duncan et al., 1997 for a review). As such, this possible implication does not seem very likely.

The second possible implication is that a global bias against contralesional targets is necessary, but not sufficient to elicit extinction. Instead, a global bias against contralesional target representations might be a common consequence of unilateral right hemispheric brain damage, but an additional factor might be required to elicit extinction. Interestingly, over the years, several authors have argued that extinction patients might not only suffer from a spatial bias against contralesional information, but also present with a pathological reduction in attentional capacity (de Haan et al., 2012; Driver et al. 1997; Karnath, 1988). The main argument here is that a spatial bias alone can explain poorer performance for contralesional targets in extinction patients, but not their complete failure to attend and respond to contralesional targets. To explain the complete failure to attend and respond to contralesional targets in extinction patients, it seems necessary to additionally postulate that these patients additionally present with a pathological (non-directional) reduction of attentional capacity.

Several recent studies have now provided evidence for this idea by showing that reducing attentional capacity in healthy subjects can elicit extinction-like behaviour (Emrich, Burianova & Ferber, 2011; Matthias et al., 2009). As such, this possible implication appears plausible. Moreover, the idea that both a spatial bias and a pathological reduction of attentional capacity are required to elicit extinction can explain both the observation from our study and previous studies (Habekost & Rostrup, 2006; Smania et al., 1998) that a contralesional processing impairment can occur independently from the presence of extinction and the observation that the severity of contralesional processing impairments can correlate with the severity of extinction (Habekost & Rostrup, 2006; Marzi et al., 1996; Schwartz et al., 1979). If a spatial bias against contralesional information is a general consequence of right hemispheric brain damage, one would expect patients in whom the spatial bias is present while extinction is not. However, one would also expect extinction severity in patients in whom the conditions for the occurrence of extinction are met to be modulated by the severity of the spatial bias. Nevertheless, direct patient evidence for a reduction of attentional capacity in extinction is currently unfortunately rather sparse. Two studies investigated attentional capacity in stroke patients, but did not assess the relationship between attentional capacity and extinction severity. They observed that stroke patients with

damage centering on the right parietal cortex show a pathological reduction of attentional capacity (Duncan et al., 1999) and that this pathological reduction of attentional capacity was particularly pronounced in patients with damage centering on the temporo-parietal junction (Peers et al., 2005). A single study that did attempted to investigate the relationship between attentional capacity and extinction severity found no correlation between these factors (Habekost & Rostrup, 2006). However, as this study predominantly assessed patients with minor or no clinical signs of extinction, this null result is difficult to interpret. Currently, the only direct evidence for the idea that extinction patients suffer from a general reduction of attentional capacity was presented in a study by Karnath (1988). He presented three extinction patients with bilateral stimuli. The patients knew stimuli were always presented bilaterally and their task was to name these stimuli. In separate experiments, these patients were either free to report the stimuli in any order or were instructed to report the contralesional left-sided stimulus first. As expected, all three patients showed contralesional extinction when free to report the stimuli in any order: they showed no impairment reporting the ipsilesional right stimulus, but were impaired reporting the contralesional left stimulus. Additionally, all three patients spontaneously reported the right ipsilesional stimulus first under this condition. Interestingly, however, when these patients subsequently were instructed to report the contralesional left stimulus first, all three patients now showed 'ipsilesional extinction', i.e. their deficit reporting the contralesional left stimulus disappeared and they were now impaired reporting the ipsilesional right stimulus. This strongly suggests the presence of a non-directional deficit of attentional capacity in extinction patients.

Taken together, the most likely interpretation of our finding that contralesional early sensory deficits can occur independently of the presence of extinction, is that a spatial bias against contralesional information is a general consequence of unilateral right hemispheric brain damage. This suggests that the presence of a spatial bias against contralesional information is not sufficient to elicit extinction. Extinction appears to additionally require a pathological reduction of attentional capacity. Nevertheless, further research is required to clarify the exact cognitive processes impaired in extinction patients.

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Figure legends

Figure 1: Lesion overlap images for the group of patients with extinction (EXT, top) and the group of patients without extinction (RBD, bottom). The number of overlapping lesions is illustrated by colour, from violet ($n = 1$) to red ($n = \text{maximum}$, i.e. the amount of patients in the group). The numbers at the bottom of the Figure indicate MNI z-coordinates.

Figure 2: A) Example of a trial in the masked visuo-motor response priming experiment. This example depicts a trial with a bilateral prime stimulus featuring an informative prime on the left and a neutral prime on the right. Moreover, the informative prime (arrow pointing up) and the subsequent central target (arrow pointing down) are incongruent. Thus, the trial type is bilateral incongruent informative prime left. B) Illustration of the stimuli used as primes in

the masked visuo-motor response priming experiment. These stimuli were additionally used as targets in the computerized extinction task.

Figure 3: Individual participant's performance accuracy in the control experiment. Grey bars denote performance accuracy to the central target, whereas the black bars left and right of the central grey bar denote guessing accuracy for prime stimuli presented in the left and right visual field respectively. The dotted red line denotes chance guessing rate for the prime stimuli (33.33%). The participant number starting with 'SUB' denotes the healthy subject, participant numbers starting with 'EXT' denote brain damaged patients with extinction and participant numbers starting with 'RBD' denote right brain damaged patients without extinction. The participant numbers of the neurological patients used here correspond to the participant numbers used in Table 1.

Figure 4: Mean reaction times (ms) to the central target for each of the trial types in the masked visuo-motor response priming experiment. The different graphs reflect the different informative prime conditions (unilateral left, unilateral right, bilateral left and bilateral right) and within each graph reaction times are shown for each prime-target congruency condition (incongruent, neutral and congruent) and participant group. Solid black lines indicate neurologically healthy subjects, dashed green lines indicate right brain damaged patients without extinction and dotted red lines indicate right brain damaged patients with extinction. Error bars reflect standard error of the mean.

Table 1: Patient characteristics

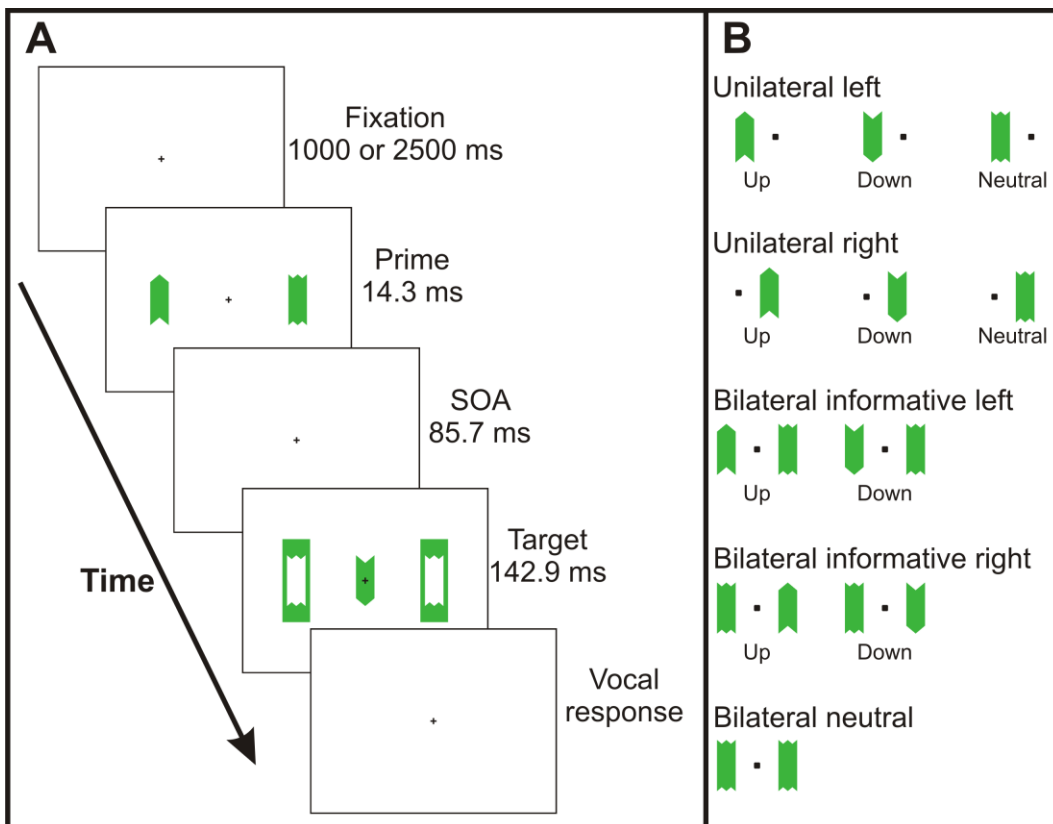
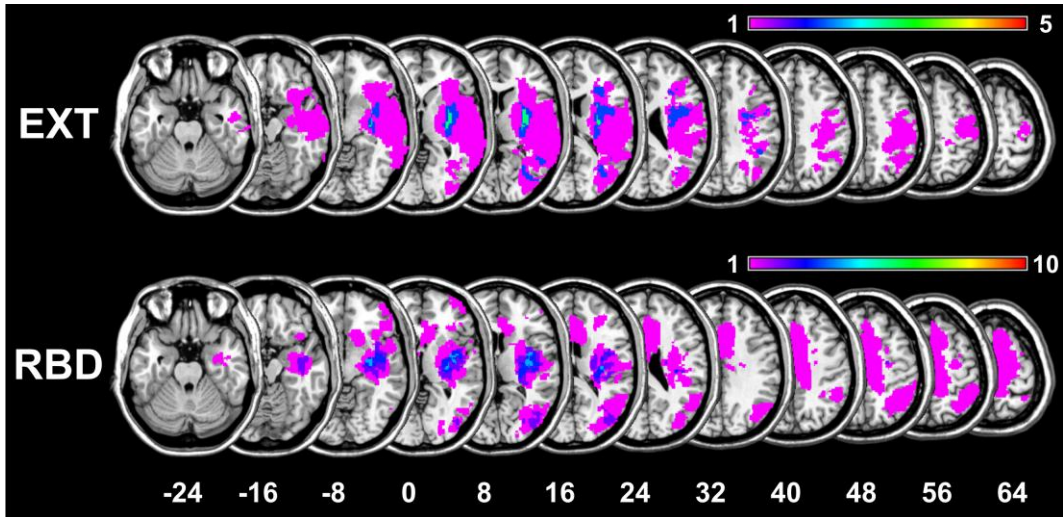
| Patient | Sex | Age | Etiology | Time between stroke and testing | Extinction | | Neglect | | | Group |
|---------|-----|---------|--|---------------------------------|------------|------------|---------|-------|---------|-------|
| | | | | | FP | COMP | Letter | Bells | Copying | |
| 5 | M | 42 yrs. | Infarct middle cerebral artery | 2 days | 0/0/90/0 | *** | 29/30 | 15/14 | *** | EXT |
| 308 | F | 84 yrs. | Infarct middle cerebral artery | 6 days | 0/0/80/0 | 0/0/100/0 | 21/26 | 7/12 | 0 | EXT |
| 317 | M | 70 yrs. | Watershed infarct middle/posterior cerebral artery | 5 days | 0/0/100/0 | 0/0/84.2/0 | 28/29 | 13/12 | 1 | EXT |
| 320 | F | 63 | Infarct middle | 6 days | 0/0/100/0 | 0/0/40/0 | 20/3 | 10/1 | 0 | EXT |

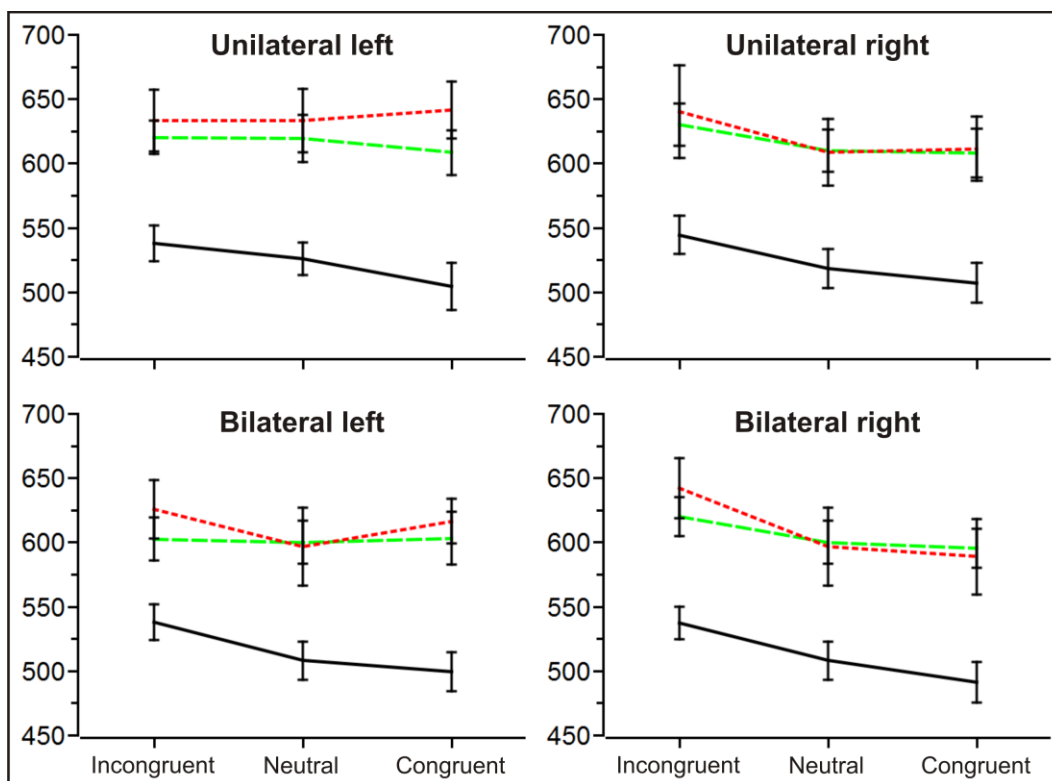
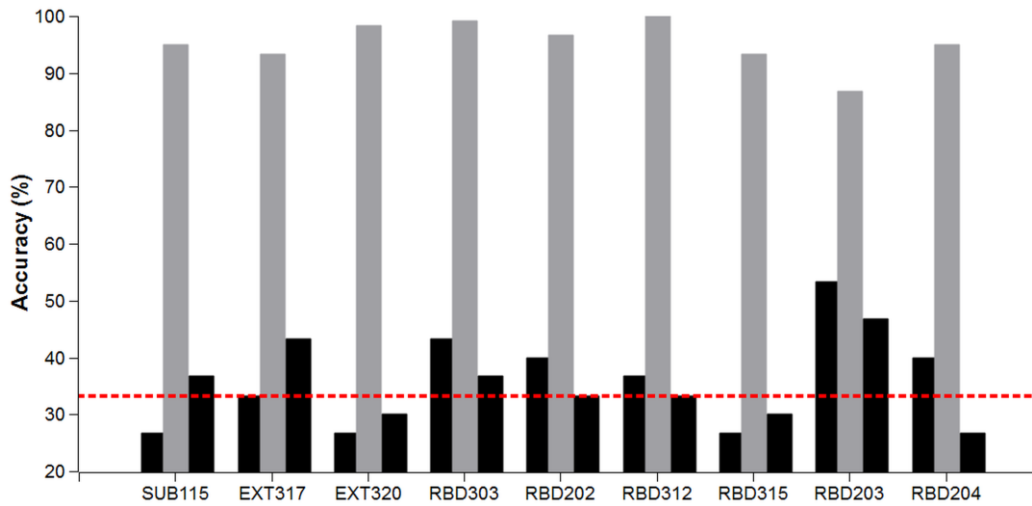
| | | | | | | | | | | |
|-----|---|------------|-----------------------------------|---------|---------------|--------------|-----------|-----------|---|-----|
| 15 | M | yrs. 74 | cerebral artery Infarct middle | 11 days | 0 0/0/50/0 | 0/0/100/0 | 0 29/3 | 5 14/1 | 0 | EXT |
| | | yrs. | cerebral artery | | | | 0 | 3 | | |
| 11 | M | 55 | Infarct middle | 5 days | 0/0/0/0 | *** | 30/3 | 14/1 | 0 | RBD |
| | | yrs. | cerebral artery | | | | 0 | 5 | | |
| 303 | M | 70 | Infarct middle | 5 days | 0/0/0/0 | 0/0/2.5/0 | 30/3 | 15/1 | 0 | RBD |
| | | yrs. | cerebral artery | | | | 0 | 2 | | |
| 202 | F | 67 | Infarct middle | 3 days | 0/0/0/0 | 0/0/0/0 | 29/3 | 9/14 | 0 | RBD |
| | | yrs. | cerebral artery | | | | 0 | | | |
| 312 | M | 50 | Infarct middle | 3 days | 0/0/0/0 | 0/0/0/0 | 30/2 | 14/1 | 0 | RBD |
| | | yrs. | cerebral artery | | | | 9 | 5 | | |
| 313 | M | 70 | Haemorrhage | 8 days | 0/0/0/0 | 8.3/0/7.5/0 | 30/2 | 13/1 | 0 | RBD |
| | | yrs. | frontal lobe | | | | 7 | 5 | | |
| 314 | M | 29 | Infarct middle | 7 days | 0/0/0/0 | 8.3/0/10.3/0 | 25/2 | 13/1 | 0 | RBD |
| | | yrs. | cerebral artery | | | | 8 | 4 | | |
| 315 | F | 61 | Haemorrhage | 4 days | 0/0/0/0 | 0/0/5.1/2.5 | 30/3 | 14/1 | 0 | RBD |
| | | yrs. | basal ganglia | | | | 0 | 5 | | |
| 316 | F | 39 | Infarct middle | 11 days | 0/0/0/0 | 0/0/0/0 | 26/3 | 12/1 | 1 | RBD |
| | | yrs. | cerebral artery | | | | 0 | 5 | | |
| 203 | M | 51 | Infarct middle | 11 days | 0/0/0/0 | 0/0/0/0 | 30/3 | 15/1 | 0 | RBD |
| | | yrs. | cerebral artery | | | | 0 | 5 | | |
| 204 | M | 50 | Infarct middle | 4 days | 0/0/0/0 | 0/0/0/0 | 30/3 | 15/1 | 0 | RBD |
| | | yrs. | cerebral artery | | | | 0 | 5 | | |
| 205 | F | 75 | Infarct middle | 11 days | 0/0/0/0 | 0/0/0/0 | 27/2 | 11/1 | 0 | RBD |
| | | yrs. | cerebral artery | | | | 9 | 4 | | |
| 206 | F | 68 | Infarct middle | 4 days | 0/0/0/0 | 0/0/0/0 | 23/2 | 11/1 | 0 | RBD |
| | | yrs. | cerebral artery | | | | 7 | 4 | | |

Legend: FP = percent omissions in fingerperimetrical assessment (unilateral left, unilateral right, bilateral left, bilateral right), COMP = percent omissions in computerized extinction task (unilateral left, unilateral right, bilateral left, bilateral right), Letter = left- and right-sided detections in the letter cancellation test (30 letters on each side), Bells = left- and right-sided detections in the bells cancellation test (15 bells on each side), Copying = points scored in the copying task (4 pictures, missing left half of a picture is 1 point, missing an entire picture is 2 points, maximum score is 8), Group = whether patient was assigned to extinction (EXT) or without extinction (RBD) group. *** denotes that this assessment was not possible in this patient.

Table 2: Mean participant accuracy (%) and standard error (in brackets) for each of the trial types and participant groups in the masked visuo-motor response priming experiment

| Group | Unilateral left | | | Unilateral right | | |
|---------|-----------------|-------------|-------------|------------------|-------------|-------------|
| | Incongruent | Neutral | Congruent | Incongruent | Neutral | Congruent |
| EXT | 100.0 (0.0) | 99.2 (0.7) | 100.0 (0.0) | 99.2 (0.8) | 100.0 (0.0) | 100.0 (0.0) |
| RBD | 99.7 (0.3) | 100.0 (0.0) | 99.7 (0.3) | 100.0 (0.0) | 99.7 (0.3) | 99.7 (0.3) |
| Healthy | 99.1 (0.6) | 99.9 (0.1) | 99.6 (0.3) | 98.1 (0.9) | 99.9 (0.1) | 99.6 (0.3) |
| Group | Bilateral left | | | Bilateral right | | |
| | Incongruent | Neutral | Congruent | Incongruent | Neutral | Congruent |
| EXT | 100.0 (0.0) | 99.2 (0.8) | 99.2 (0.8) | 100.0 (0.0) | 99.2 (0.8) | 100.0 (0.0) |
| RBD | 99.7 (0.3) | 100.0 (0.0) | 99.7 (0.3) | 99.3 (0.4) | 100.0 (0.0) | 100.0 (0.0) |
| Healthy | 99.7 (0.3) | 99.8 (0.1) | 100.0 (0.0) | 98.9 (0.5) | 99.8 (0.1) | 99.4 (0.3) |





Highlights

- Early processing of contralesional stimuli is reduced after right brain damage
- This deficit occurs regardless of the presence or absence of extinction
- Suggests contralesional sensory weakening general consequence of right brain damage
- Extinction might additionally require reduction in attentional capacity

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