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Re-fixation and perseveration patterns in neglect patients during free visual exploration

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Abstract

The literature suggests that neglect patients not only show impairments in directing attention towards the left, contralesional space, but also present with perseverative behavior. Moreover, previous studies described re-fixations during visual search tasks, and interpreted this finding as an impairment of spatial working memory. The aim of the present study was to study re-fixations and perseverations (i.e., recurrent re-fixations to same locations) during free visual exploration, a task with high ecological validity. We hypothesized that: (1) neglect patient would perform re-fixations more frequently than healthy controls within the right hemispace; and, (2) the re-fixation behavior of neglect patients would be characterized by perseverative fixations. To test these hypotheses, we assessed 22 neglect patients and 23 healthy controls, measuring their eye movements during free exploration of naturalistic pictures. The results showed that neglect patients tend to re-fixate locations within the ipsilesional hemispace when they freely explore naturalistic pictures. Importantly, the saliency of discrete locations within the pictures has a stronger influence on fixation behavior within the contralesional than within the ipsilesional hemispace in neglect patients. Finally, the results indicated that, for re-fixations, saliency plays a more important role within the contralesional than the ipsilesional hemispace. Moreover, we found evidence that re-fixation behavior of neglect patients is characterized by frequent recurrent re-fixations back to the same spatial locations which may be interpreted as perseverations. Hence, with the present study, we could better elucidate the mechanism leading to re-fixations and perseverative behavior during free visual exploration in neglect patients.

Accepted Article

Introduction

Unilateral spatial neglect is defined as the inability to attend or respond to the contralesional hemispace, whereby this inability is not due to primary sensory or motor deficits (Kleinman et al., 2013). In severe cases, neglect patients act as if the contralesional hemispace no longer exists (Karnath et al., 2002). Besides the typical symptoms concerning the contralesional hemispace, there is evidence that behavior within the ipsilesional hemispace is also affected (Halligan et al., 1992; Kleinman et al., 2013; Manly et al., 2002; Mannan et al., 2005; Na et al., 1999; Nys et al., 2006; Rusconi et al., 2002). For instance, repeated cancellations of targets in cancellation tasks, or excessive and repetitive graphic productions in drawing tasks, may occur within the ipsilesional hemispace (Kaufmann et al., 2018; Manly et al., 2002; Nys et al., 2006). These perseverative phenomena are frequently observed in neglect patients, occurring in 30% (Na et al., 1999) to 90% (Rusconi et al., 2002) of the patients. Furthermore, when eye movements are recorded during visual search tasks, frequent re-fixations within the ipsilesional hemispace have also been described (Husain et al., 2001; Manly et al., 2002). The tendency of neglect patients to re-fixate locations within the ipsilesional hemispace has been interpreted on the background of different cognitive mechanisms, such as perseverative behavior, hyperattention to or deficient attentional disengagement within the ipsilesional hemispace, deficits in inhibition of return, or impairments in spatial working memory (Müri et al., 2009). For instance, an earlier study highlighted the important role of spatial working memory in visual search tasks, since neglect patients not only re-fixated previously found targets, but also misjudged already fixated targets as new (Mannan et al., 2005).

Saliency plays an important role for the spatial distribution of fixations during visual exploration. When examining gaze patterns and re-fixation behavior in healthy subjects using naturalistic pictures (visual search or free visual exploration), the saliency of discrete regions of the images may play an important role: regions with higher saliency are per se more likely to be fixated, and are thus also more likely to be more frequently re-fixated (Bays & Husain, 2012). Previous findings suggest that the visual exploration patterns of neglect patients and healthy controls are differentially affected by saliency (Fellrath & Ptak, 2015; Ossandón et al., 2012; Ptak et al., 2009; Ptak & Müri, 2013). In neglect patients, saliency seems to affect the fixation behavior more strongly in the contralesional than in the ipsilesional hemispace (Fellrath & Ptak, 2015). Visual re-fixation behavior of neglect patients has mostly been investigated in visual search tasks with artificial stimuli, i.e. arrays of target and distractor objects, and not naturalistic pictures. However, results from visual search tasks cannot be directly translated to free visual exploration tasks. For instance, in visual search tasks using artificial stimuli, equally salient targets are most commonly evenly distributed in space, whereas, in free visual exploration of naturalistic photographs, discrete regions with unequal saliency are unevenly distributed in space. To the best of our knowledge, visual re-fixation behavior during free visual exploration has not yet been investigated in neglect patients. The assessment of re-fixation behavior during free exploration of naturalistic pictures is of great relevance, since it more closely reflects everyday situations than visual search in arrays of artificial stimuli. Hence, new insights concerning the re-fixation behavior of neglect patients during free visual exploration has the potential to more accurately reflect their deficits in everyday functioning.

In the present study, we aimed to analyze re-fixations and their spatial distribution in neglect patients during the free visual exploration of naturalistic pictures. Furthermore, we were interested in assessing whether neglect patients would show perseverations, i.e., perseverative fixations. Fixations were termed perseverative, if they fell back to a spatial location that was already re-fixated at least once (location fixated at least three times; see Figure 1). We hypothesized that: a) neglect patients would show a higher probability of re-fixations within the ipsilesional hemispace than healthy controls; b) neglect patients would show more frequent perseverations than healthy controls; and, c) compared to healthy controls, in neglect patients, saliency would play a more important role within the contralesional than the ipsilesional hemispace, for fixations as well as for re-fixations.

Materials and methods

Participants

22 patients suffering from left-sided visual neglect after a first, right-hemispheric stroke (age: mean = 56.68 years, standard deviation = 9.49, range between 32 and 70; sex: 40.91% female), and 23 healthy age and gender matched controls (age: mean = 62.09 years, standard deviation = 17.66, range between 31 and 91; sex: 52.17% female) participated in the present study. All participants gave written informed consent, and the study was carried out in accordance with the latest version of the Declaration of Helsinki. The study was approved by the Ethics Committees of the states of Bern and Lucerne.

To assess visual neglect, the Line Bisection Task (Wilson et al., 1987) was performed. In addition, the Centre of Cancellation (CoC; i.e., the center of mass of the spatial distribution of cancelled items; Rorden & Karnath, 2010) was determined based on the results of the Bells test (Gauthier et al., 1989), the Star Cancellation test (Wilson et al., 1987), or the Random Shape Cancellation test (Weintraub & Mesulam, 1988). The patients were defined as presenting with visual neglect if the mean relative rightward deviation from the actual midline in the Line Bisection Task was at least 11% (Wilson et al., 1987) or if the CoC value was greater than 0.08 (Rorden & Karnath, 2010). In order to avoid confounding effects of hemianopia or quadrantanopia, only patients with an intact central 30° of their visual field were included in the present study.

Stimuli and procedure

The participants performed a free visual exploration task. 48 images (1024 x 768 pixels) were presented on a computer monitor (17 inches), comprising 24 photographs of natural scenes or urban public places, and their 24 mirrored versions (mirrored along the central vertical axis of the image). The photographs did not contain any text, and only few architectural images included humans (e.g., people sitting in front of a cathedral). The images were presented in a random order, for 7 seconds each. A central white fixation cross on a black screen, presented for 1 second, preceded the presentation of each picture. The participants were seated in front of the computer monitor, their head positioned on a chin-and-forehead rest, ensuring that the midsaggital plane of the participants was aligned with the middle of the screen, at a constant distance of 60 cm, resulting in a viewing angle of 32 x 24°.

Using a computational model (Itti et al., 1998), a saliency map was separately computed for each of the 48 used images. This model uses color images as input. The features are calculated by linear center-surround filters, similar to the visual receptive fields, resulting in feature maps of these center-surround differences. The model computes 6 maps for intensity, 12 maps for color, and 24 maps for orientation. These feature maps are then combined into single conspicuity maps for intensity, color, and orientation. It is assumed that these modalities independently contribute to the saliency of a particular region of an image; the three conspicuity maps are thus normalized and summed up into a single saliency map, with values ranging from 0 to 1. The most salient location within an image is thereby defined as the maximum value within the saliency map.

Eye movements were recorded using a remote, infrared-based eye tracking system (T120, Tobii Technology, Stockholm, Sweden). Fixations shorter than 100 ms were excluded from the analyses (Carpenter, 1988; Salthouse & Ellis, 1980), which resulted in the exclusion of 3.5% of all the fixations made within the screen (total number of fixations collected: n = 35'124). An independent samples t-test revealed no significant difference between the number of excluded fixations for healthy controls (M = 2.61%, SE = .61) and neglect patients (M = 4.39%, SE = 1.18; $t(43) = 1.359$, $P = .181$).

Response variables

Firstly, to ascertain whether patients showed signs of visual neglect in the free visual exploration task, we analyzed the spatial distribution of visual fixations over the horizontal axis. To this end, we calculated correlations between the horizontal position (i.e., the visual angle in degrees) and the number of fixations within the images. For this analysis we only included the horizontal position of the fixations, however, in all of the ensuing analyses, both the horizontal and the vertical positions were taken into account.

The primary focus of the present study was re-fixation behavior. A re-fixation was defined as a fixation that landed within an area of one degree visual angle with respect to at least one previous fixation (i.e., Euclidean-distance ≤ 32 pixels). We examined the re-fixation rate (i.e., the number of re-fixations divided by the number of fixations). The re-fixation rate was calculated for every participant over all images, separately for the left and the right hemifield (the first fixation in each image being excluded from analysis). In a next step, we examined re-fixations on the same location. To this end, we extended the definition of single re-fixations to groups of re-fixations, i.e., a re-fixation was considered to belong to a group of re-fixations on the same location if it landed within an Euclidean distance of 32 pixels from at least one re-fixation in the group. In accordance with this definition, we categorized single re-fixations into groups of re- fixations on the same location using hierarchical cluster analyses with single linkage (i.e., the distance between clusters is equal to the minimum distance between two observations). We further assessed a specific type of re-fixations, namely perseverative fixations, thought to reflect perseverative behavior. Perseverative fixations were fixations that fell back to a spatial location that was already re-fixated at least once (location fixated at least three times). Based on this definition, we examined the proportion of perseverative fixations with respect to the total number of re-fixations (*perseveration rate*); this analysis was applied to images in which participants presented at least two re-fixations. The perseveration rate was calculated for every participant, averaged over all images. An example of the procedure is shown in Figure 1.

Other response variables were the hemifield (left or right) where the first re-fixation was made, and the number of fixations preceding the first occurring re-fixation. For the number of fixations until the first re-fixation, there were right-censored data values (the event of interest did not occur), i.e., images in which a specific participant did not make a re-fixation until the end of the presentation. For the right-censored data values, the total number of fixations at the end of the presentation of the corresponding image was included in the analysis. Finally, we were also interested in the role of the saliency of the locations on which fixations and re-fixations occurred (measured with the computational model by Itti et al., 1998). For all participants, the mean saliencies of fixated and re-fixated locations were calculated in the left and right hemifield for every image.

Statistical analysis

The statistical analyses were performed using R (R Foundation for Statistical Computing, Vienna, Austria). For all statistical tests, we used a significance level of α=5%. For the effects concerning our hypotheses, we calculated one-tailed p-values; for all other effects, we used two-tailed p-values. When comparing response variables between different combinations of factors, the p-values were adjusted with the Bonferroni- Holm method, in order to account for multiple testing. As predictors, we included the between-subject factor “group” (neglect patients or healthy controls, neglect patients as reference category), the within-subject factor “hemifield” (left or right, left as reference category), and the within-subject factor “type of fixation” (re-fixation or fixation on new location, fixations on new locations as reference category).

Firstly, to ascertain whether patients showed left-sided neglect signs in the free visual exploration task, we analyzed the relationship between the number of fixations and their horizontal position. We quantified the rightward shift in the spatial distribution of the number of fixations for every participant and compared it between the two groups. To this end, the possible range of values for the visual angle (i.e., from -16° to 16°) was divided into 10 columns of equal width, coded from 1 to 10, where 1 represented the leftmost and 10 the rightmost part of an image. For all subjects, we calculated a Spearman's rank correlation coefficient between the horizontal position, as reflected by the coded columns, and the number of fixations in the corresponding column for every image. These correlations were transformed using *Fisher's Z-Transformation*. The Z-transformed values were analyzed using a Linear Mixed-Effects Model (*LMM*), with a fixed effect for the factor “group”, to test for differences between neglect patients and healthy controls. The LMM contained random intercepts for all participants and images as random effects, to take into account correlations of the data points within subjects and images.

Additionally, for the neglect patients, Pearson’s correlations were calculated to investigate whether there was a relationship between neglect severity (i.e., the performance on the line bisection task and the CoC) and the number of fixations in the left and right hemifield, respectively.

In an ensuing step, the re-fixation and perseveration rates were analyzed using permutation tests. We calculated t- statistics for paired (comparison of the hemifields) or unpaired (comparison of the groups) samples and determined the approximative distribution of the t-statistics under the null-hypothesis (no difference between the means) and calculated the corresponding approximative p-value using 10’000 random permutations of the data. The interaction effect between “group” and “hemifield” on the re-fixation rate was tested as follows: (1) for every participant the difference between the hemifields was calculated ($mean_{right} – mean_{left}$), (2) for these unpaired samples (neglect patients and healthy controls) the t-statistic was calculated and (3) the approximative p-value was determined by drawing 10’000 random permutations from the data. Moreover, we compared the re-fixation rate between the groups for both hemifields separately and between the hemifields for both groups separately. For the perseveration rate, we compared the overall rate between the two groups. In addition to the above-mentioned analyses, for the neglect patients, Pearson’s correlations were calculated to investigate whether there was a relationship between neglect severity (i.e., the performance on the line bisection task and the CoC) and the number of re-fixations in the left and right hemifield, respectively, as well as the perseveration rate.

The response variable "hemifield of the first re-fixation" was analyzed using a Logit Mixed-Effects Model (*Logit-MM*), with a fixed effect for the group and a random intercept per subject and image. The number of fixations preceding the first re-fixation was modelled using a Cox Mixed-Effects Model (*Cox-MM*), which enables the inclusion of uncensored data values. The Cox-MM included a fixed effect for the group and a random intercept per subject and image. With this Cox-MM, we could compare the hazard rates between the groups, whereby it was more likely that the first re-fixation occurred earlier for the group with the higher hazard rate than for the group with the lower hazard rate. For our response variable, the hazard rate at a value x is the risk of occurrence of the first re-fixation after x fixations. In a next step, we analyzed the mean saliency of the fixated regions using a LMM. The LMM contained fixed effects for the factors group, hemifield, and type of fixation, all second-order interaction effects, and the third-order interaction effect of the three factors, as well as random intercepts per subject and image. We tested the third-order interaction effect to assess whether the difference in the mean saliency of the regions, in which fixations on new locations and re-fixations occurred, would depend on the combination of group and hemifield.

Results

Neglect in the free visual exploration task

Figure 2 shows the number of fixations during free visual exploration, indicating that the spatial distribution of fixations in neglect patients showed a shift towards the right side of the screen (mean visual angle of 5.53°, corresponding to 684.79 pixels). For healthy subjects, the number of fixations was symmetrically distributed over the horizontal axis, with a mean visual angle of -0.12° (corresponding to 508.66 pixels). The model with the Z-transformed correlations as response variable revealed significantly lower mean Z-values for healthy participants than for neglect patients (two-tailed test; $t_{42.98} = -9.96$, $P < .001$). The estimated correlation between the horizontal position for neglect patients was 0.55, which is significantly higher than 0 (two-tailed test; $t_{48.76} = 13.14$, $P < .001$). For healthy participants, the estimated correlation was -0.02, and did not significantly differ from 0 (two-tailed test; $t_{48.81} = -0.34$, $P = .734$). These results show that, for neglect patients, the number of fixations increased along the horizontal axis from the left to the right end of an image, whereas, for healthy subjects, there was no relationship between the number of fixations and their distribution on the horizontal axis. Pearson's correlations revealed no significant relationship between line bisection values or CoC and the number of fixations in the left and right hemifields, respectively (all P's >.05).

Re-fixation and perseveration rates

For the re-fixation rate, we found a significant interaction effect between group and hemifield (two-tailed test; $t = 4.38$, $P < .001$). This interaction is visualized in Figure 3a. In the right hemifield, the mean re-fixation rate was significantly lower for healthy participants than for neglect patients (one-tailed test; $z = -2.74$, $P = .003$, $P_{adj} = .008$), whereas this difference was reversed in the left visual field (two-tailed test; $z = 3.50$, $P = .003$, $P_{adj} = .008$). Moreover, for healthy participants, there was no significant difference between the mean re-fixation rates in the two hemifields (two-tailed test; $z = -0.95$, $P = .341$, $P_{adj} = .341$), whereas the mean re-fixation rate was significantly higher within the right than the left hemifield for neglect patients (two-tailed test; $z = 4.16$, $P < .001$, $P_{adj} = .002$).

Furthermore, we were interested in specifically assessing the re-fixation rate in the early visual exploration phase. When considering the first 10 fixations during free visual exploration, the interaction between group and hemifield was significant (two-tailed test; $t = 4.93$, $P < .001$). This interaction during the early visual exploration phase is depicted in Figure 3b. As for the analysis with the complete dataset, healthy controls showed a significantly lower mean re-fixation rate for the right hemifield (one-tailed test; $z = -4.30$, $P < .001$, $P_{adj} < .001$), and a significantly higher mean re-fixation rate for the left hemifield (two-tailed test; $z = 2.78$, $P = .010$, $P_{adj} = .020$), as compared to neglect patients. In contrast to the analysis with the complete data set, healthy controls had a significantly higher mean re-fixation rate for the left compared to the right hemifield (two-tailed test; $z = -2.45$, $P = .024$, $P_{adj} = .024$), whereas neglect patients showed a significantly higher mean re-fixation rate for the right compared to the left hemifield (two-tailed test; $z = 4.31$, $P < .001$, $P_{adj} = .001$).

In general, the mean perseveration rate was significantly lower for healthy controls than for neglect patients (one-tailed test; $z = -1.98$, $P = .030$). For neglect patients, the mean perseveration rate was 18.31%, whereas it was 14.25% for healthy controls. Pearson's correlations revealed no significant relationship between line bisection values or CoC with the overall perseveration rate, as well as no significant relationship with the re-fixation rate (neither for the first 10 re-fixations nor for the total data set) in the left and right hemifields, respectively (all *P*'s >.05).

The first re-fixation

For the response variable concerning the hemifield in which the first re-fixation occurred, we found that the mean probability of a first re-fixation within the right hemifield was significantly lower for healthy participants than for neglect patients (two-tailed test; $z = -9.02$, $P < .001$). For neglect patients, there was a strong tendency to make their first re-fixation within the right hemifield. The estimated probability of a first re-fixation within the right hemifield was 93.5%, which was significantly above chance (i.e., 50%; two-tailed test; $z = 10.57$, $P < .001$). For healthy participants, there was no evidence for a tendency to preferentially produce a first re-fixation within the right or the left hemifield. The estimated probability of a first re-fixation within the right hemifield was 45.1%, which did not significantly differ from chance (two-tailed test; $z = -1.02$, $P = .308$). In a further step, we assessed the number of fixations preceding the first re-fixation. We found that neglect patients had a significantly higher mean hazard rate than healthy participants (two-tailed test; $z = -2.67$, $P = .008$). Hence, it was significantly more likely that neglect patients would re-fixate in an earlier phase of the visual exploration than healthy controls.

The saliency of fixated and re-fixated locations

In a next step, we fitted a model with the mean saliency values as response variables. The model revealed a significant interaction effect between the group, the hemifield, and the type of fixation (two-tailed test; $z = 2.08$, $P = .038$). Hence, this result provides evidence that the difference in the mean saliencies between re-fixated and newly fixated locations depends on the combination of the factors group and hemifield. To further analyze this interaction, we compared the mean saliencies of specific combinations of the three factors (see Figure 4). For neglect patients, the mean saliency values of re-fixated regions within left hemifield was significantly higher than the one of newly fixated regions (one-tailed test; $z = 2.75$, $P = .006$, $P_{adj} = .015$); in contrast, there was no significant difference within the right hemifield (two-tailed test; $z = 1.55$, $P = .122$, $P_{adj} = .380$). For healthy controls, the mean saliency values of re-fixated regions were significantly higher than the ones of newly fixated regions within the right hemifield (two-tailed test; $z = 3.13$, $P = .002$, $P_{adj} = .012$), whereas there was no significant difference concerning the left hemifield (two-tailed test; $z = 1.67$, $P = .095$, $P_{adj} = .380$). For neglect patients, the mean saliency values of newly fixated regions were significantly higher within the left than the right hemifield (two-tailed test; $z = -2.83$, $P = .005$, $P_{adj} = .028$). There were no significant differences for healthy controls (two-tailed test; $z = -0.60$, $P = .545$, $P_{adj} = .743$). The same was true for re-fixations (two-tailed test; neglect patients: $z = -3.62$, $P < .001$, $P_{adj} = .002$; healthy participants: $z = 0.893$, $P = .372$, $P_{adj} = .743$).

Discussion

The aim of the present study was to examine the re-fixation behavior in patients with left-sided neglect and healthy controls during a free visual exploration task. We analyzed the spatial distribution of fixations and found, as expected, that patients with left-sided neglect showed a rightward shift in this distribution. Furthermore, neglect patients showed a significantly higher re-fixation rate than healthy controls within the ipsilesional hemispace, even when only the early phase of visual exploration was considered (i.e., the first ten fixations). Moreover, for neglect patients, re-fixations occurred significantly earlier than for healthy controls, with a strong tendency for the first re-fixation to occur within the ipsilesional hemispace. By analyzing the role of saliency, we found evidence that, in neglect patients, fixations and re-fixations within the contralesional hemispace occurred in regions of the images with significantly higher mean saliency values. Finally, the perseveration rate was significantly higher in neglect patients than in healthy controls.

As expected, neglect patients showed the typically observed rightward shift in attentional spatial allocation (Cazzoli et al., 2010, 2011; Fellrath & Ptak, 2015; Müri et al., 2013; Nyffeler et al., 2008; Ossandón et al., 2012; Pflugshaupt et al., 2004; Ptak et al., 2009; Ptak & Müri, 2013). The main focus of the present study was to assess re-fixation behavior. Previous studies have examined re-fixation behavior with visual search tasks, and found that neglect patients tend to re-fixate items within the ipsilesional hemispace during visual search (Husain et al., 2001; Mannan et al., 2005). In contrast to these studies, we used naturalistic pictures as stimuli, which better reflect visual exploration in everyday situations. Using this free visual exploration paradigm, we found that neglect patients also showed higher re-fixation rates within the ipsilesional hemispace. Interestingly, the effects were still present even when only the first ten fixations were included in the analysis. Hence, this indicates that the difference between neglect patients and healthy controls is not the result of an accumulation of fixations due to limited explored area within the ipsilesional hemispace. Moreover, we found that neglect patients had higher probabilities to re-fixate earlier compared to healthy controls, as well as to re-fixate for the first time within the ipsilesional hemispace.

Since the present study used naturalistic pictures as stimuli, it was possible to examine the role of the saliency of discrete regions of the pictures in triggering re-fixations. To assess the saliency of regions, saliency maps were computed by means of the model by Itti et al. (1998). Previous studies showed that the effects of saliency on visual exploration are different in neglect patients and healthy controls (Fellrath & Ptak, 2015; Ossandón et al., 2012; Ptak & Müri, 2013). For instance, Fellrath and Ptak (2015) found that, in neglect patients, the fixated regions showed higher saliency values in the contralesional than in the ipsilesional hemispace. In agreement with the results of this study, we found that the saliency of fixated locations was higher in the contralesional than in the ipsilesional hemispace. As a new finding, our results also indicate that, in neglect patients, re-fixations fall on locations with higher saliencies in the contralesional than in the ipsilesional hemispace. Furthermore, when only considering the contralesional hemispace, the saliency of regions being re-fixated was even higher than the one of regions that were fixated for the first time. In contrast, we found no evidence for an influence of saliency on re-fixation rates within the ipsilesional hemispace. Hence, our results further highlight the importance of saliency in guiding visual exploration behavior in neglect patients and demonstrate that this influence is specific to the contralesional hemispace. In fact, if a stronger reliance on saliency per se (i.e., across the whole space) would explain the re-fixation behavior of neglect patients, this should have also led to repeated fixations on locations with high saliency within the ipsilesional hemispace, a prediction that is not supported by our results.

Finally, we aimed to assess perseverative fixations in neglect patients. Previous studies (Halligan et al., 1992; Kaufmann et al., 2018; Kleinman et al., 2013; Manly et al., 2002; Mannan et al., 2005; Na et al., 1999; Nys et al., 2006; Rusconi et al., 2002) showed that neglect patients have the tendency to perform repetitive behavior within the ipsilesional hemispace. Such repetitive behavior is often classified as perseverative, but different definitions and types of perseverations have been proposed in the literature (Gandola et al., 2013). Perseverations in neglect patients have been often assessed by means of re-cancellations (i.e., repetitive markings of visual targets) in standard paper-and-pencil cancellation tasks (Rusconi et al., 2002). For instance, a previous study administered to neglect patients different, modified versions of standard re-cancellation tasks, and showed a significant influence of visual feedback (i.e., visible or invisible markings) on re-cancellations, especially when targets only differ in their spatial location and not in other aspects like shape or size (Wojciulik et al., 2001). Furthermore, several studies (Husain et al., 2001; Mannan et al., 2005) used computerized visual search tasks with eye-tracking, which resembled standard cancellation tasks, but in which the detection of a target had to be acknowledged by the patients only by means of a visual fixation on it (i.e., without an explicit graphic marking). In the study by Mannan et al. (2005), a similar visual search task was used, and participants were instructed to click a button whenever they would fixate an item for the first time. Re-fixations as well as "re-clicks" (i.e., misjudging previously searched locations as new) were analyzed, and the results provided evidence that re-fixation behavior in neglect patients during visual search may be caused by an impairment of spatial working memory. Compared to our study, there are important methodological differences. In the present study, we used a free visual exploration task. In contrast to visual search, during free visual exploration, no explicit task instructions (concerning, e.g., target identity and location of previously detected targets) have to be held in working memory. Furthermore, we used naturalistic pictures instead of artificial stimuli. During free visual exploration of pictures, spatial locations can be remembered by means of cues with a less prominent spatial nature (e.g., color, size or form). Moreover, targets in visual search tasks are usually of similar saliency and homogenously distributed across space, whereas, in free visual exploration tasks, different regions of the pictures present differing saliency values and are non-homogenously distributed within the pictures. Thus, the underlying mechanisms leading to re-fixations in free visual exploration, as in the present study, may be different to the ones taking place during visual search. To contrast possible sources of re-fixations in neglect patients (i.e., an impaired spatial working memory versus perseverative behavior), we defined a new type of re-fixations, namely perseverative fixations. We found that, in relation to the total number of re-fixated locations, the proportion of locations containing perseverative fixations is higher in neglect patients. This result suggests that, compared to healthy participants, the re-fixation behavior in neglect patients is characterized by frequent perseverative fixations. If the difference in re-fixation behavior between neglect patients and healthy participants would be solely due to impaired working memory, re-fixations would be expected to show the same pattern as fixations on new locations, which would ultimately lead to a similar number of recurrent re-fixations on the same location for both patients and healthy participants. This, however, was not the case in our study, thus further suggesting different mechanisms underlying our findings and the ones of other studies using visual search tasks.

In conclusion, the present study provides new insights regarding re-fixations and perseverations in neglect patients. Our results suggest that neglect patients show a tendency to re-fixate locations within the ipsilesional hemispace when they freely explore naturalistic pictures. Moreover, the re-fixation pattern observed in neglect patients during early visual exploration points towards a non-adaptive oculomotor behavior, since neglect patients re-fixate previously visited locations instead of first exploring the whole available visual space. Furthermore, in accordance with the results of earlier studies, we found that the saliency of discrete regions of the pictures has a stronger influence on fixation behavior within the contralesional than within the ipsilesional hemispace in neglect patients. The results of the present study indicate that the saliency of these locations plays a more important role within the contralesional hemispace also for re-fixation behavior. Moreover, the present study proposed a new definition of perseverations (i.e., perseverative fixations), which revealed useful to further examine the sources of re-fixation behavior in neglect patients, allowing to contrast the role of perseverations and impairments of spatial working memory in leading to re-fixation behavior.

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Conflict of Interest Statement

The authors declare no conflicts of interest.

Author Contributions

Patric Wyss wrote the manuscript under supervision of René Müri and analyzed the data together with Rebecca Paladini. Both Rebecca Paladini and Brigitte Kaufmann helped to interpret the results. Rebecca Paladini revised the manuscript, and Brigitte Kaufmann also wrote parts of the manuscript. Prabitha Urwyler was involved in processing the study data and implemented the study tasks. Dario Cazzoli carried out the study. René Müri and Thomas Nyffeler planned the study with the help of Tobias Nef. Moreover, René Müri and Thomas Nyffeler both provided accessibility to the participants of the study. René Müri supervised the project with the help of Thomas Nyffeler and Tobias Nef. All authors discussed the results and were involved in the final manuscript.

Data Accessibility

All relevant data and codes supporting the findings in this paper are available upon request.

Abbreviations

CoC	Center of Cancellation
Cox-MM	Cox Mixed-Effects Model
LMM	Linear Mixed-Effects Model
Logit-MM	Logit Mixed-Effects Model

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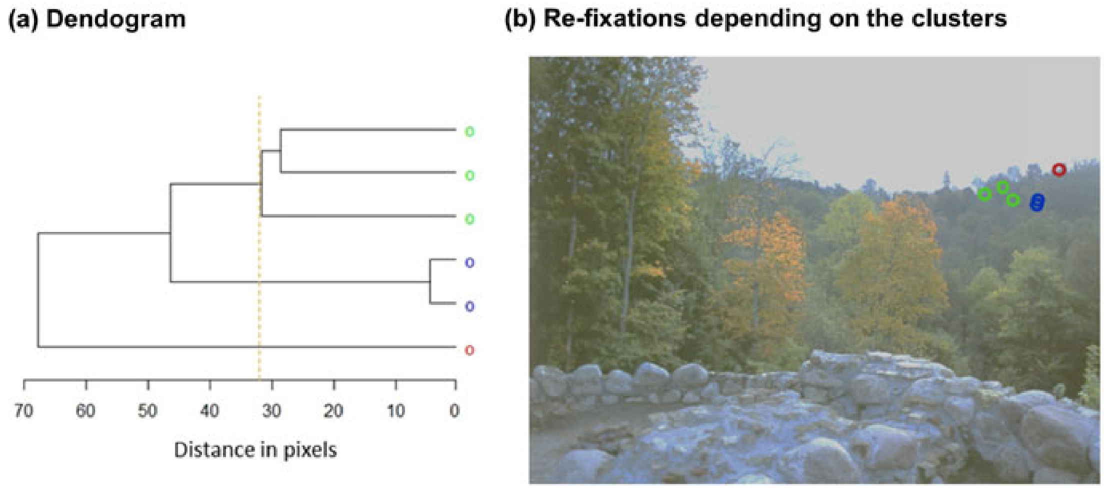
Figure captions

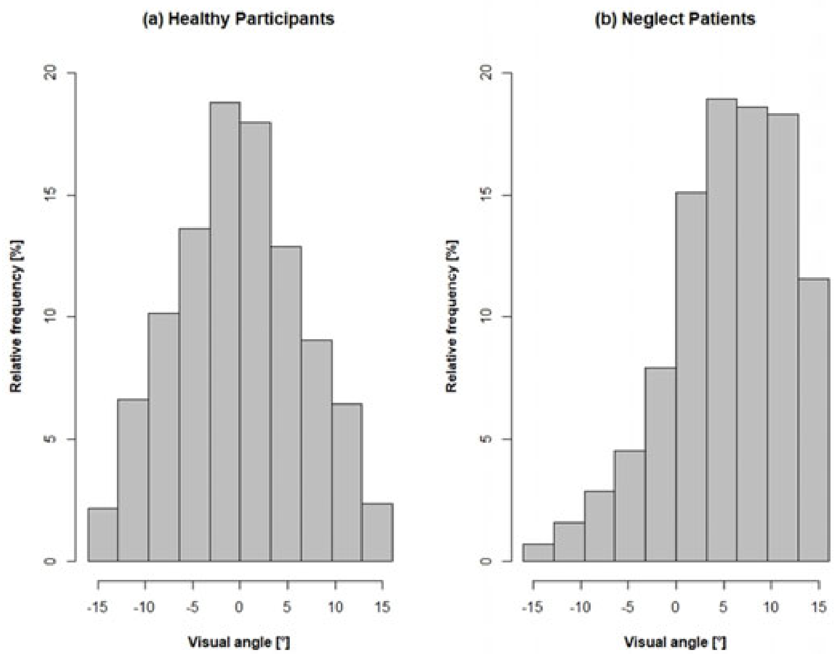
Figure 1. Exemplary depiction of how the number of re-fixations on the same location was determined in a neglect patient. (a) Dendrogram of the re-fixations for a cluster analysis with Euclidean-distance and single linkage. The dotted line at a distance of 32 pixels cuts the dendrogram into three clusters. Hence, re-fixations are considered to be on three locations, whereas the patient performed in total 3 perseverative fixations distributed over two locations (2 within the green and one within the blue re-fixations). This corresponds to a perseveration rate of 50% (3 perseverative fixations out of 6 re-fixations). (b) Plot of the re-fixations (color corresponding to the clusters in (a)). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

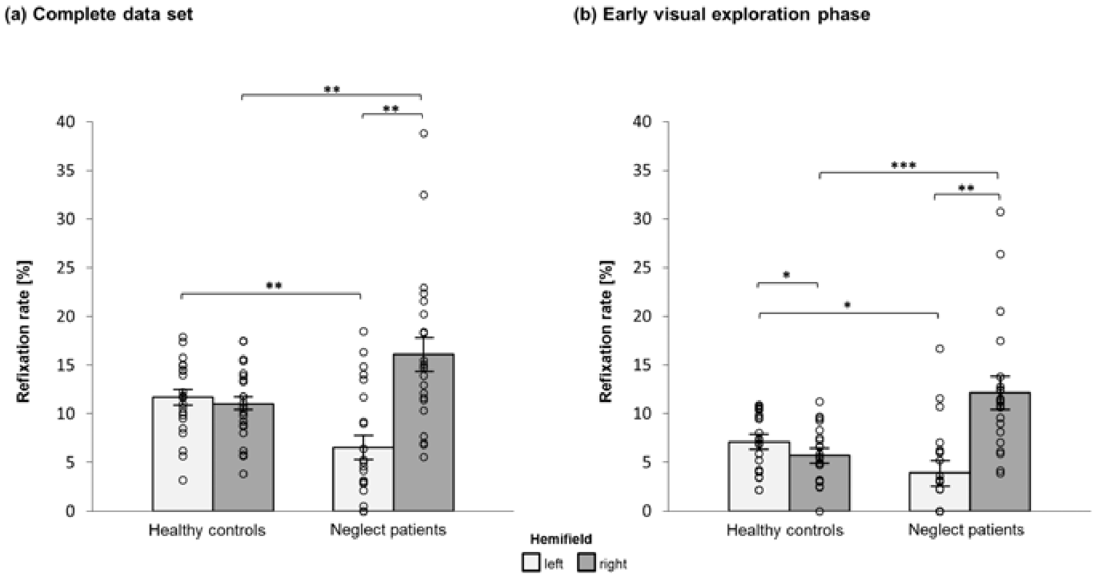
Figure 2. Histograms depicting the number of fixations on the horizontal axis (expressed in visual angle), separately for (a) healthy participants, and (b) neglect patients.

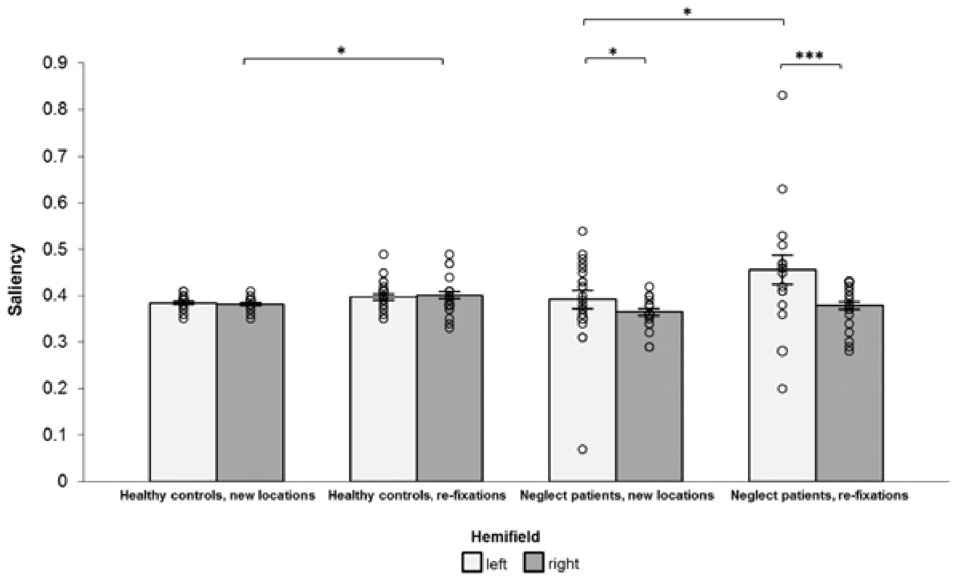
Figure 3. Mean re-fixation rate (± 1 standard error) for (a) the complete data set and (b) the data set containing only the first ten re-fixations. (*$p<.05$, **$p<.01$, ***$p<.001$) according to group, as well as the corresponding individual mean re-fixation rates.

Figure 4. Estimated mean saliencies (± 1 estimated standard error of the mean; *$p<.05$, **$p<.01$, ***$p<.001$) according to group and type of fixation, as well as the estimated individual mean saliencies.


(a) Dendogram
(b) Re-fixations depending on the clusters
70 60 50 40 30 20 10 0
Distance in pixels


(a) Healthy Participants
(b) Neglect Patients
Relative frequency [%]
Visual angle [°]
0
5
10
15
20
-15
-10
-5
0
5
10
15


(a) Complete data set
(b) Early visual exploration phase
Refixation rate [%]
0
5
10
15
20
25
30
35
40
Healthy controls
Neglect patients
**
*
***
Hemifield
left
right



*
*
*
***
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
Saliency
Healthy controls, new locations
Healthy controls, re-fixations
Neglect patients, new locations
Neglect patients, re-fixations
Hemifield
left
right