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Diagnosing Gaze and Arrow Cueing Effects in Unilateral Spatial Neglect

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30 **Abstract**

31 Individuals with left unilateral spatial neglect (USN) following a right hemisphere lesion
32 show difficulty in orienting their attention toward stimuli presented on the left. In normal
33 cognition, others' gaze direction and a pointing arrow naturally guide visual attention. Here
34 we explore a method to identify patients who may benefit from these skills as a base for
35 compensation during rehabilitation. To this end, we tested gaze and arrow cueing effects in 26
36 healthy participants (control group) and in 13 patients with USN. We calculated z-scores to
37 reference individual patients' performance to the mean performance of the control group. We
38 found high heterogeneity among patients. In the left (i.e. neglect) field, we identified two
39 patients who were unable to complete the task, three patients who responded to Gaze only,
40 one who responded to Arrows only, four who responded to both Gaze and Arrows, and three
41 Non-responders. Moreover, for the patients, we found a correlation between the effect sizes
42 for gaze and arrow cueing in the right but not in the left field. Our data show that brain
43 injuries causing USN do not affect gaze and arrow cueing in a consistent manner from one
44 patient to another. We lay the ground for developing a tool to diagnose the presence of gaze
45 and/or arrow cueing in patients with USN.

46

47 **Keywords:** left unilateral spatial neglect, brain lesion, gaze cueing, arrow cueing, diagnosing

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1. Introduction

Unilateral spatial neglect (USN) involves a difficulty to detect, respond to or orient one's attention toward stimuli presented to (or represented on) the contralateral side of a brain lesion, which is usually located in the right hemisphere (Heilman, Watson, & Valenstein, 1993). Clinical forms of USN are very heterogeneous (Vuilleumier and Saj, 2014). Yet, one major characteristic of USN is that patients present difficulties in “consciously” and/or “unconsciously” orienting attention to the left space (Corbetta & Shulman, 2011). Since attention plays a major role in perception and cognition, allowing one to search for, detect and learn about relevant sensory stimuli, USN hampers individuals' ability to recover their autonomy (Bowen, Hazelton, Pollock, & Lincoln, 2013). To reduce USN, several rehabilitation techniques have been proposed (Luauté, Halligan, Rossetti, Rode & Boisson, 2006). However, in a Cochrane review, Bowen et al. (2013) highlighted the limited effect of these techniques for daily activities and the need to rely on patients' preserved abilities in future rehabilitation methods.

In daily social interactions, others' gaze direction naturally guides visual attention (Csibra & Gergely, 2009). In experimental settings with adults, this is typically reflected by faster reaction times at detecting a visual target that appears at the location where a face is looking relative to visual targets in another location (for a review Frischen, Bayliss, & Tipper, 2007). Although pointing arrows convey a similar cueing effect, gaze is more powerful. Gaze direction is coded even when it is completely irrelevant and potentially interferes with the task (Zorzi, Mapelli, Rusconi, & Umiltà, 2003). Accordingly, the gaze cueing effect occurs in 70% of cases in which gaze points in the wrong direction. By contrast, when an arrow is pointing in the wrong direction, the arrow cueing effect vanishes (Driver et al., 1999). The gaze cueing effect seems particularly difficult to inhibit, probably because others' gaze is highly informative very early in human cognitive development (Csibra & Gergely, 2009). Thus, the

gaze cueing effect could be a relevant tool to help patients with USN explore their neglected field. However, current research on USN predicts a high heterogeneity in the perseverance of the gaze cuing effect among patients. Here, we lay the foundation for developing a tool to identify patients with USN who respond to gaze cueing toward their neglected field. We aim to identify patients who might benefit from this skill as a form of compensation during rehabilitation.

To our knowledge, only two studies have investigated the gaze cueing effect in patients with USN. In the pioneer study, Vuilleumier (2002) reported a gaze cueing effect in four patients with right parietal damage and USN. According to the authors, schematic gazes helped the patients orient attention toward both the right and left sides. By contrast, arrows helped attention orienting toward the right side, but not toward the neglect side. This study suggested a specific benefit of gaze cueing in these four patients. More recently, Bonato, Priftis, Marenzi, & Zorzi (2009) presented 17 right hemisphere lesion patients (9 with USN) with centrally symbolic cues (arrows and numbers) and schematic eye gaze cues. In contrast to Vuilleumier (2002), patients mostly oriented spatial attention with arrows (not numbers) and only patients without USN oriented spatial attention from gaze cueing. These divergent results may reflect the heterogeneity of patients' brain lesions causing USN.

In recent decades, numerous neuroimaging studies have demonstrated that spatial orienting is implemented in bilateral networks involving parietal, temporal and frontal cortical regions, as well as subcortical structures such as thalamus, superior colliculus and basal ganglia (He, Shulman, Snyder & Corbetta, 2007; Ringman, Saver, Woolson, Clarke, & Adams, 2004), with a stronger specialization of the right hemisphere (Bartolomeo, Thiebaut de Schotten, & Chica, 2012; Corbetta & Shulman, 2011; He et al, 2007). Theoretically, a lesion in those large right networks may cause USN (Ringman et al, 2004). Meta-analyses confirm that cortical and subcortical regions of this network have consistently been associated with spatial neglect

100 symptoms (Molenberghs, Sale, & Mattingley, 2012; Chechlacz, Rotshtein, & Humphreys,
101 2012; Vuilleumier, 2013). However, these analyses also reveal that disruption of fiber tracts
102 that enable cortico-cortical connections or subcortico-cortical connections between distinct
103 components of the spatial networks contribute to USN. Moreover, impaired inter-hemispheric
104 communication may also contribute to neglect symptoms (e.g. Lunven et al, 2015). The wide
105 range of brain lesions causing USN likely explains the high heterogeneity of behavioural
106 symptoms that are observed in that disorder (Molenberghs et al., 2012; Chechlacz et al, 2012).
107 The neural mechanism underlying USN can be dynamically modulated by either endogenous
108 or exogenous signals (Leal Rato, Mares, Aguiar de Sousa, Senju, & Pavao Martins, 2019).
109 Endogenous orienting refers to voluntary shifts of attention (i.e. top-down mechanisms),
110 while exogenous orienting refers to stimulus-driven and automatic orienting of attention (i.e.
111 bottom-up mechanisms). Several studies have investigated the brain mechanisms underlying
112 gaze and arrow cueing effects and reported that these effects do not fully share common brain
113 substrates. While gaze has been associated with an exogenous signal, arrows have been
114 associated with an endogenous signal preferentially recruiting frontal regions (Hietanen,
115 Nummenmaa, Nyman, Parkkola, & Hämäläinen, 2006; Lockhofen, Gruppe, Ruprecht,
116 Gallhofer, & Sammer, 2014). Moreover, the gaze cueing effect would involve the temporo-
117 parietal junction, superior temporal sulcus, inferior parietal lobule, fusiform gyrus,
118 middle/inferior frontal gyrus and possibly subcortical structures such as the superior
119 colliculus and the amygdala, regions that are often described in the right hemisphere (e.g.
120 Akiyama et al., 2006; Greene & Zaidel, 2011; Sato, Kochiyama, Uono, & Toichi, 2016; Zhao,
121 Li, Uono, Yoshimura & Toichi, 2017). Arrows would preferentially activate the occipital
122 gyrus, the right frontal eye field and supplementary eye field (Hietanen et al., 2006;
123 Lockhofen., et al., 2014), most often, bilaterally (e.g. Greene & Zaidel, 2011). What is
124 currently known about the brain correlates of USN and cueing effects predicts a high

heterogeneity in patients' capacity for responding to gaze and/or arrow cueing in their neglect space. Here, we tested a statistical method that discriminates between patients with and without this capacity.

The statistical treatment of single-case study data is one area of methodology that has been relatively neglected (e.g. Crawford, Garthwaite^b, & Howell, 2009). The most common method consists in referencing patients' performance to a matched control sample. The statistical analysis of such data usually uses z-scores (i.e. signed numbers of Standard Deviation –SD- by which individual values are above or below the mean value of a control group). Patients' performance is converted to a z score based on the control group's mean and SD and this z value is referred to a table of areas under the normal curve. Here, we used this approach to determine whether a given patient responds to gaze and/or arrow cueing. In our study, we used a standard Posner-like attention orienting paradigm (Posner, 1980) where the gaze and arrow are alternatively used as a central attentional cue.

2. Methods

2.1.Participants

A total of 39 right-handed native French-speaking participants were included in the study: 13 patients with a diagnosed left USN secondary to right brain damage (9 females, mean age = 64.7 years \pm 9.6) and 26 healthy control elderly participants (16 females; mean age=66.4 years \pm 10.0)¹. The patients with left USN were recruited from the neurological rehabilitation unit of “Centre de reeducation et de réadaptation fonctionnelles Le Bourbonnais UGECAM BFC” at Bourbon Lancy (France). All participants provided written informed consent according to

¹ For the control group, we replicated the sample size used in most recent studies investigating gaze and arrow cuing effects in both control participants and patients with brain damage (Dalmaso, Castelli, Priftis, & Galfano, 2015; Bonato et al, 2009).

institutional guidelines of the local research ethics committee (which is in compliance with the Declaration of Helsinki). The whole procedure was approved by the local ethics committee (CPP Est I, approval n° 2016-A01433-48). A full description of the patient group is presented in Table 1. Inclusion criteria of both participant groups are provided in Tables 1 and 2, respectively.

(Table 1 about here)

(Table 2 about here)

2.2. Stimuli

2.2.1. Gaze cues

Face stimuli consisted of 40 static color photographs of 20 individuals (10 males/10 females) selected from a database of digitized portraits of adult faces (see Conty, N'Diaye, Tijus, & George, 2007). All faces were of individuals unknown to our participants and had a neutral expression. Head direction was always oriented straight toward the observer. Each individual was presented in two different views: one with the eyes directed straight toward the observer (Direct Gaze), and one with the eyes averted 30° toward the right side of the observer's position (Averted Gaze). To avoid any unintended differences in picture backgrounds, the eye region in the averted gaze stimuli was cut and pasted into the very same position within the photographs used for the direct gaze stimuli. Next, for all stimuli (including Direct Gaze faces), left sides were obtained by mirror-imaging. All stimuli were presented in 256 colors and reduced to a height of 310 pixels and a width of 148 pixels while preserving their proportion. During the experiment, the face stimuli covered a visual angle of approximately 7.5° vertically and 6° horizontally.

2.2.2. Arrow cues

Arrows were created using Photoshop CS5.1. Three pictures were created. The first picture represented a white bar measuring 112 pixels (width) x 12 pixels (height) superimposed on a white circle (\varnothing 56 pixels). The second and third pictures were the same but with an arrow pointing toward the right or left instead of the bar. These objects were designed to cover the faces' eye region, i.e. approximatively a visual angle of 1.5° vertically and 3° horizontally.

2.2.3. *Target*

The target stimulus consisted of a white asterisk displayed in bold Arial Font, 42-point, and covered a $0.5^\circ \times 0.5^\circ$ visual angle.

2.3. *Procedure*

Participants sat approximately 60 cm in front of a Terra computer with a 15.6-inch screen (with a resolution of 1366 x 768 pixels) on which stimuli were shown on a black background. E-Prime® 2.0 software was used to control stimulus presentation, response recording and latency (Psychology Software Tools, 2002). The height of the screen was adjusted so that the middle of the screen was aligned with participants' eyes.

The experiment was divided into two 100-trial sequences with a break after 50 trials. We used 3 main conditions: Gaze (40 trials per sequence), Arrow (40 trials per sequence) and Neutral (20 trials per sequence). In each sequence, trial presentation was randomized across participants. Each trial started with a 500 ms presentation of a fixation cross located at the level of the stimulus face's eyes (in the Gaze condition) and bar (in the Arrow condition). Then, a face with a direct gaze (or the bar) appeared on the screen. After 900ms, the face was replaced by the same face gazing to the right (in half of the trials) or to the left. Thus, in the Gaze condition, participants viewed a face in which the eyes moved away from him/her. In the Arrow condition, the bar was replaced by the arrow pointing to the right (in half of the trials) or to the left. In the Neutral condition, the fixation cross remained on the screen during

the whole trial. However, the cross became red between 500 and 900 ms following its appearance and then turned white again. Therefore, the Neutral condition contained the same timing as the Gaze and Arrow conditions (Fig. 1).

In each trial, 500 ms after the previous event, the target stimulus appeared at 9° visual angle on the right (in half of the trials) or on the left. The target was aligned with the face's eye direction and/or with the arrow. Participants had to indicate as fast and correctly as possible whether the target appeared on the left or on the right by pressing one of the two corresponding mouse buttons. Once the subject responded or after 3500ms, a black screen appeared and remained for 900 ms before the next trial. Participants were informed that the face and arrow images preceding the target were not informative for the task. The experiment began with two practice trials that were not analyzed.

(Figure 1 about here)

2.4. Statistical analyses

2.4.1. Group analysis

We computed the Percentage of Correct Responses (%CR) and the Reaction times of the correct responses (RTs). Separately for each group (Patients and Controls), these variables were submitted to a repeated measures analysis of variance (ANOVA) with Field of target appearance (Left vs. Right), Cue (Gaze vs. Arrow) and Cue Direction (Congruent vs. Incongruent) as between-subjects factors. Planned comparisons were performed when interactions were observed. When effects were reported, we provided mean performances and Standard Errors (SE) obtained in each condition.

2.4.2. Standard effect sizes of the control group

RTs of the control participants were averaged across Fields. For each type of cue (Gaze and Arrow) we computed two standard effect sizes (SES): SES 1 = [RTs for the Neutral condition – RTs for the Congruent condition] and SES 2 = [RTs for the Incongruent condition – RTs for the Congruent condition]. The normality of these effects was tested with the Kolmogorov-Smirnov Test and significance was tested with a two-tailed t-test against 0.

2.4.3. Individual patient analysis

The SES analyses in the control group revealed that (Gaze and Arrow) SES 1 were statistically more robust than (Gaze and Arrow) SES 2 (see results). For each patient, each cue (Gaze and Arrow) and each field (right/left), we thus computed ES 1 = [RTs for the neutral condition – RTs for the congruent condition] to identify Gaze and/or Arrow responders. We converted the results into standard scores (Z-scores Z_i) using the mean (\bar{X}) and the standard deviation (S) from the control group: $Z_i = \frac{X_i - \bar{X}}{S}$. To ensure that z-scores were reliable we checked that each patient's performance was above chance in each condition used for calculating the z-score. Moreover, as the experiment was divided in two sequences of 100 trials each (see method), we computed patients' z-score for each sequence.

2.4.4. Correlation analyses

We tested the correlation between Gaze and Arrow SES1 independently for control participants and patients. For patients, the test was performed twice (for the left and right fields). Since three correlations were calculated, significance was set at $p < .016$. For each group, we provide the Pearson's R and bilateral p -values.

2.4.5. Regression analyses

We tested whether patients' performance in the neglect field was predicted by the post-brain injury delay and/or their performance on the neuropsychological tests used to diagnose UNS

severity. We fitted standard general linear models (GLM) to RTs in the left field (all conditions confounded), %CR in the left field (all conditions confounded), ES 1 and z-scores of Gaze and Arrow. Each of these 6 GLMs included five regressors of interest: the post-brain injury delay (in months), the deviation (in millimeters) measured with the Line Bisection test, the difference in number of omissions between the left and right side on Bell's Test, and on the Visual Field Test and Neglect subtests of the TAP.

3. Results

3.1.Group Analysis

3.1.1. Control group

The ANOVA run on RTs showed a main effect of Cue Direction ($F(1,25)=10.59$; $p<0.01$). Control participants were faster on Congruent (mean RTs = 510 ± 17) versus Incongruent trials (mean RTs = 535 ± 19). No other effects or interactions were observed. The ANOVA run on %CR revealed no main effects or interactions. Control participants performed well on all conditions (mean %CR = 99 ± 0.5).

3.1.2. Patients

The RT analyses showed a main effect of Field ($F(1,12)=20.91$; $p<0.001$). Patients were faster at detecting the target when it appeared on the right (mean RTs = 920 ± 73) versus the left (mean RTs = 1339 ± 111). We also observed a main effect of Cue Direction ($F(1,12)=8.80$; $p=0.011$). Patients were faster for Congruent (mean RTs = 1008 ± 67) versus Incongruent trials (mean RTs = 1251 ± 111). Importantly, there was an interaction between Field and Cue ($F(1,12)=6.38$; $p=0.026$). Post-hoc analyses showed that the effect of Cue Direction was greater in the left field ($p<.0001$; mean effect size = 322 ± 112) than in the right ($p=0.04$; mean effect size = 135 ± 46). No other main effects or interactions were observed for RTs.

The ANOVA run on %CR showed a main effect of Field ($F(1,12)= 5.29$; $p=0.04$). Patients performed better in the right field (mean %CR = 94 ± 1) than the left (mean %CR = 79 ± 6). Cue Direction failed to reach significance ($F(1,12)=3.91$; $p=0.07$). However, the interaction between Field and Cue Direction reached significance ($F(1,12)=5.32$; $p=0.04$). Post-hoc analyses revealed that patients performed better on Congruent than Incongruent trials but only in the left field ($p<0.003$ – effect size= $10\%\pm5$).

(Table 3 about here)

(Figure 2 about here)

3.2.Standard effect sizes in the control group

We then computed standard effect sizes (SES) of Gaze and Arrow cueing (see analyses). For each cue, we tested the normality and the significance of each SES: SES 1 = [RTs for the Neutral condition – RTs for the Congruent condition] and SES 2 = [RTs for the Incongruent condition – RTs for the Congruent condition]. The analyses revealed that SES 1 did not diverge from a Gaussian distribution and differed significantly from 0 for both Gaze and Arrow (see Table 4 for details). SES 2 did not diverge from a Gaussian distribution either, but failed to reach significance for Gaze (see Table 4 for details). Further analyses revealed that SES 1 was larger than SES 2 for Gaze ($t=3.91$; $p<0.01$) but not for Arrow ($p=.16$). Altogether, these results revealed that SES 1 was a more relevant standard of the cueing effects than SES 2 (especially for Gaze).

(Table 4 about here)

3.3.Individual patient analyses

Usually, z values below -1.65 or above +1.65 are considered to deviate significantly from the normal score. This method allows researchers to test for a deficit in the single case. Here, however, the purpose is not to test for a deficit, but for the presence of an effect. A z -score of 0 corresponds to the mean cueing effect observed in the control group, which significantly differed from 0. In others words, $z > 0$ indicates the presence of a cueing effect. We thus applied a cut-off of $z > 0$ to determine the presence of cueing effects.

However, to ensure the reliability of the diagnosis, only patients showing z -scores > 0 in both sequences were identified as responders. Moreover, z -scores were considered reliable only for patients whose performance was above chance ($> 50\%$) in each condition used for the calculation (Neutral and Congruent conditions, separately for left and right fields). This resulted in the exclusion of two patients from the left field analyses: GA (mean %CR = 30% in the left and 99% in the right) and TJ (mean %CR = 32% in the left and 93% in the right - see Table 5). Interestingly, two other patients (BR and to a lesser extend LC) showed difficulty when the target appeared on the left but only when the cues were incongruent (i.e. pointing on the right; mean %CR for BR = 30%; mean %CR for LC = 50% - see Table 5). As incongruent trials were not used for computing z -scores, these patients were not excluded from the z -score analyses.

(Table 5 about here)

Applying these criteria to the left field, we identified two patients unable to perform the task (GA and TJ), four Gaze and Arrow responders (RM, VP, BMC and BR), three responders to Gaze only (KF, LC and LJ), one responder to Arrows only (MMT), and three non-responders (DMC, SD and DCJ) (see Table 1, Table 6 and Figure 3 for patient profiles). In the right field, we identified three Gaze and Arrow responders (GA, BMC and LC), one responder to Gaze

only (BR), four responders to Arrows only (VP, LJ, DCJ and MMT) and five Non-responders (TJ, DMC, KF, RM and SD).

(Table 6 about here)

(Figure 3 about here)

3.4. Correlations and regression analyses

At the group level, we found positive correlations between Gaze ES1 and Arrow ES1 in the control group ($r=0.62$; $p=.001$). Most importantly, in the patient group, this correlation was significant in the right field ($r=0.67$; $p=.012$) but not the left ($r=0.43$; $p=.14$).

Regression analyses revealed that the performance of patients in the left field (RTs all condition confounded, %CR all conditions confounded, ES 1 and z-scores for Gaze and Arrow) was not predicted by the post-brain injury delay, by performance on the neuropsychological tests, or by the interaction between these variables (all $ps>0.05$).

4. Discussion

We explored a method for identifying patients with USN who respond to gaze cueing and/or arrow cueing toward their neglected field and who might benefit from this skill as a form of compensation during rehabilitation. Using a standard Posner-like attention orienting task where gaze or arrows were used as a central cue, we first performed classical group analyses in 26 control participants and 13 patients with USN.

We observed a benefit of both gaze and arrow cueing in the control group. On average, participants were faster at detecting the target in the congruent condition (vs. incongruent and neutral). These effects did not depend on the type of cue or the field in which the target appeared, contrary to what some authors have reported (Driver et al., 1999; Marotta,

Lupiañez, & Casagrande, 2012). Interestingly, we reproduced a classic finding that has mainly been reported in young participants. Our results converge with those of Slessor, Phillips, & Bull (2008) who found that older participants (65-79 years old) respond to both gaze and arrow cueing, albeit less so than younger participants.

At the group level, the analyses confirm USN in the group of patients, who performed worse (both on RTs and %CR) when the target appeared in the left field (vs. the right). Importantly, not only did the patients present a cueing effect (for gaze and arrow confounded), but this effect was stronger when the target appeared in the left as compared to the right field (see Dalmaso et al, 2015, for similar results in patients with right-hemisphere damage without USN). This shows that, on average, patients spontaneously used the central cue when it helps to orient attention toward the neglected side. Our results diverge from Vuilleumier (2002)'s study showing that gaze but not arrow helped their four patients to orient attention toward their neglected (left) field and Bonato et al. (2009)'s study showing that arrow but not gaze helped their nine patients to orient attention toward their neglected (left) field. We argue that these divergent results come from the high heterogeneity observed among the brain lesions causing USN.

The analyses run at the individual level confirm this hypothesis. We computed standard gaze and arrow cueing effects (RTs for the Neutral condition – RTs for the Congruent condition) from the control group. The patients' cueing effects were also computed and converted to z -scores based on the control group's means and SDs. Using a cut-off of $z > 0$ at the individual scale, we identified, in the left field, 3 responders to Gaze only, 1 responder to Arrows only, 4 Gaze and Arrow responders, and 3 Non-responders (for a total of 11 patients whose performance in the left field allowed z -score computation). The low rate of left Non-responders observed in this study strengthens the view that gaze and/or arrow cueing effects may be a relevant tool during rehabilitation.

355 Statistical models such as individual ANOVAs may be applied at the individual level to
356 determine the presence or absence of an effect (e.g. Akiyama, 2006). Such models are
357 difficult to apply in patients due to null responses on some trials and/or the need for a high
358 number of trials. Z-scores are easier to manipulate and allow one to use a relatively low
359 number of trials. However, the reliability of this approach needs to be verified. For that
360 purpose, we stated first that the z-score may be computed only if the task was performed
361 above chance in the conditions used for the computation. In this respect, two patients (GA and
362 TJ) showed very low performance in the left (but not in the right). These results indicate that
363 our design allows for the detection of a specific impairment in perceiving exogenous stimuli
364 appearing on the left, and may be used together with other neuropsychological tests to
365 diagnose the severity of USN. Also, to avoid false positives, we ensured that z-scores showed
366 test-retest reliability. Z-scores were thus computed twice per patient, once per experimental
367 sequence. Only the patients showing a $z\text{-score} > 0$ in each sequence were identified as
368 responders. Obviously, further tests are needed to verify the test-retest reliability of the tool
369 that we propose to develop (e.g. Kaplan & Saccuzzo, 2017). However, this has to be done
370 once a more suitable version of the tool is developed (see below).

371 To identify the responders, we initially computed two standard effect sizes (SES) as a proxy
372 of cueing effects in the control population. Computing the difference between the Neutral and
373 Congruent conditions (SES 1) has several advantages. First, analyses revealed that SES 1 was
374 larger and statistically more robust than the difference between Congruent and Incongruent
375 conditions (SES 2), especially for gaze cue. This is because on average, control participants
376 were faster when cues were present (irrespective of their congruency) when compared to
377 absent, an effect that has been reported by other authors (e.g. Vuilleumier, 2002; Friesen &
378 Kingstone, 1998). Second, this allows us to design a diagnostic tool using only congruent and
379 neutral trials. Such a test would be shorter to administer and would allow us to discard any

impairments of disengagement that may be associated with incongruent cues, especially among patients (see Bonato et al., 2009). In this respect, two patients (LC and BR) presented an impairment in attentional disengagement from the right (i.e. low %CR in that particular condition where the target appeared on the left but the cue pointed to the right). Such a profile suggests we should avoid incongruent stimuli to diagnose cueing effects. Third, focusing on the effect of congruency (independently of effect of incongruency) is more rational in the context of a therapeutic approach, as incongruent gazes could disturb patients.

In the right field, we identified one responder to Gaze only, four responders to Arrows only, three Gaze and Arrow responders, and five Non-responders (for a total of 13 patients). Moreover, three patients were Gaze responders in the left but not in the right field; similarly, three patients were Arrow responders in the left but not in the right field. Interestingly, this strongly suggests that these participants spontaneously use gaze and/or arrow cues to explore the neglected field but not the other side. In other words, some patients are able to spontaneously develop strategies to compensate for their disorders. However, the number of patients that did not respond to at least one cue on the right is higher than expected. This reactivates the debate of the reflexive nature of gaze and/or arrow cueing effect which has been left open (e.g. Vecera & Rizzo, 2006, Hietanen et al., 2006).

We found a correlation between the effect sizes for gaze and arrow cueing in the control group. Importantly, for the patients, this correlation was significant in the right but not in the left field. This converges with the view that Gaze and Arrow cueing are not subtended by the same brain substrates and that a right brain injury causing USN may affect one of these but not the other. Focusing on the pathophysiological profiles of our four categories of patients (Gaze responders, Arrow responders, Gaze and Arrow responders and Non-responders), we do not have enough data to determine which brain lesions lead to which profiles (see Table 1). Moreover, regression analyses did not reveal any relation between the gaze cueing effect and

the post-brain injury delay or results on classical neuropsychological tests. This may be related to the heterogeneity in the post-brain injury delay in our sample of patients. Our first move was to test an individual statistical approach. However, in our sample, some patients with USN had a long post-brain injury delay and may have developed palliative strategies with or without rehabilitation, relying on their preserved brain substrates. Future investigations are needed to determine the profile of patients who respond to gaze and/or arrow cueing.

Finally, we chose to use real portraits of adult faces for ecological concerns, as previously done by Driver et al (1999), Bayliss et al. (2006), Bayliss et. al (2007), and Sato et al (2016) in healthy subjects and Insch et al. (2017) in patients with Alzheimer's disease. In contrast, studies conducted with patients with USN used only schematized eyes (Bonato et al, 2009) or faces (Vuilleumier, 2002; Akiyama et al, 2006) or digitalized faces (Dalmaso et al, 2015), which may also explain some of the differences in the results. Natural faces seem to motivate healthy persons to follow gaze direction (Bayliss et al, 2006). However, in our study, the target was a white asterisk. It would be interesting to use real objects of the environment to increase the ecological dimension of our test (Bayliss et al., 2006).

5. Conclusions

This study highlights the feasibility of developing a tool for identifying gaze (and/or arrow) cueing in patients suffering from USN. Comparing patients' performance to a standard effect measured in the healthy population allows one to identify the patients who voluntarily or involuntarily use (and thus may benefit from) others' gaze and/or arrow direction to explore their neglected field and who may benefit from this skill during rehabilitation. The next step will be to shorten the test and increase its ecological validity. Future investigations are also needed to determine which right brain lesions affect gaze and arrow cueing, respectively, in USN.

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547 **Tables and figures**

Table 1. Patient characteristics. Left USN diagnosis was based on clinical observation, lesion localization, and behavioral and neuropsychological tests (see Table 1). Patients were excluded if they were deemed unable to understand task instructions, if they had multiple brain lesions, or a history of psychological or psychiatric disorders. Patients underwent a neuropsychological evaluation testing episodic memory with the RL/RI-16 items (Van Der Linden et al, 2004), executive functions with the Grefex Battery (Godefroy, 2008), attentional functions with the TAP (Zimmermann & Fimm, 2010) and instrumental functions with the VOSP Test, visuo-constructive reproduction and DO80 (Deloche & Hannequin, 1997). Neglect symptoms were tested with the Bell Test, the line bisection and the Ogden scene from “Batterie d’Evaluation de la Négligence Unilatérale du Geren” (BEN, Azouvi et al, 2002). Moreover, we used two subtests from the TAP (Zimmermann & Fimm, 2010) to further support the diagnosis: visual field examination and examination of visual field “neglect condition”. Sex (F = female; M = male); Laterality (R = right-handed; Amb = ambidextrous); Etiology (TBI = traumatic brain injury); Isch = ischemia; Hem = hemorrhage; MD: motor deficit (0 = absent; 1 = monoparesis; 2 = incomplete hemiparesis; 3 = complete); SD: somatosensory deficit (0 = absent; 1 = superficial; 2 = incomplete superficial and deep; 3 = complete); LHH: left homonymous hemianopia (A = absent; P = present; NE: not analyzable); L-F bell’s omissions: difference in omissions between the left and right fields on the Bell’s Test (positive value = more omissions on the left; negative value = more omissions on the right); Line Bisection deviation in millimeters (positive value = deviation toward the right; negative value = deviation toward the left); Visual Field TAP L-F omissions: difference in omissions between the left and right fields on the TAP “Visual Field” sub-test (positive value = more omissions on the left; negative value = more omissions on the right); Neglect TAP L-F omissions: difference in omissions between the left and right fields on the TAP “Neglect” sub-test (positive value = more omissions on the left; negative value = more omissions on the right). For the sake of clarity, patients were grouped as a function of their ability to respond (1) or not (0) to Gaze cue and/or Arrow cue in their neglected (left) field (see results); Two patients who were unable to perform the task in their neglect field were labeled as N/A; Pathological scores on neuropsychological tests are indicated with *.

Case	Left Gaze Responder	Left Arrow Responder	Sex	Age in years	Laterality	Etiology	Lesion	Delay (In months)	LHH	L-F bell's omissions	Line Bisection deviation (mm)	Visual Field TAP L-F omissions	Neglect TAP L-F omissions
GA	N/A	N/A	H	73	R	isch	Lateral sulcus	2.5	NE	8*	4	15*	7*
TJ	N/A	N/A	F	61	R	TBI	frontal	2.5	A	-1	17*	2*	1
RM	1	1	F	69	Amb	hem	Lenticular nucleus	13	P	6*	7*	8*	13*
BR	1	1	F	73	R	isch	Parieto-occipito-frontal	1	NE	13*	26*	6*	13*
VP	1	1	M	54	R	TBI+isch	Fronto-temporo-parietal	11	P	4*	2.5	2*	13*
BMC	1	1	F	59	R	hem	Capsulo-thalamic	1.5	P	8*	9.5*	0	7*
KF	1	0	F	50	R	isch	Fronto-parietal	2	A	10*	9.5*	0	9*
LC	1	0	F	72	R	isch	temporal	15	P	9*	0,5	2*	6*
LJ	1	0	F	66	R	hem	temporal	1.5	A	2*	0	4*	2*
MMT	0	1	F	84	R	isch	temporal	1	A	14*	4	8*	6*
SD	0	0	M	54	R	isch	Fronto-temporo-parietal + sub-cortical	19	A	0	-8.5*	0	6*
DCJ	0	0	H	60	R	isch	Fronto-parietal-sub-cortical	2	A	5*	-5	0	7*
DMC	0	0	F	66	R	hem	Parieto-temporal + Lenticular nucleus	7	P	11*	6*	4*	11*

Table 2. Gender, education level and age (mean± standard error) of the UNS and control groups. Control participants had no neurologic or psychiatric history. To be included, participants needed to score below 5 on the Geriatric Depression Scale 15-items (Clément, Nassif, Léger, & Marchan, 1997) and above the 5th percentile on the Mini Mental State Examination (Kalafat, Poitrenaud & Hugonot-Diener, 2003). Healthy participants were matched to UNS groups for age, gender distribution, and socio-cultural level (three levels, following Godefroy, 2008). The analyses revealed that age and education level across groups did not diverge from a Gaussian distribution (Kolmogorov-Smirnov Test) and did not differ significantly between patients and control participants. All participants had normal or corrected-to-normal vision and were naive to the aim of the experiment.

	Gender	Education level	Age
UNS Group	9F/4M	1.08±0.28	64.7 ± 9.6
Control Group	16F/10M	1.69±0.95	66.4 ± 10.0
t-Test	-	t ₃₇ =-1.82; p=0.08	t ₃₇ =-0.52; p=0.61

Table 3. Percentage of correct responses and standard error (SE) for the control group (upper part) and the patients with USN (bottom part) on all experimental conditions. Control participants performed at ceiling on all conditions. Patients performed better in the right field, and their performance in the left field was better on Congruent versus Incongruent trials.

% Correct responses		Left Field		Right Field	
		Congruent	Incongruent	Congruent	Incongruent
Control Group	Gaze Cueing	99±0.4	98±0.8	99±0.3	98±0.7
	Arrow Cueing	99±0.4	98±0.4	99±0.4	99±0.3
	Neutral	98±0.8		99±0.4	
Patients	Gaze Cueing	84±6.6	75±6.9	94±1.9	93±1.9

Arrow Cueing	84±5.9	73±9.2	96±1.6	94±1.8
Neutral	74±8.5		93±2.6	

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583 **Table 4.** Standard Effect Sizes (SES) for Gaze and Arrow cues (mean±SD). SES 1= [RTs for the
584 Neutral condition – RTs for the Congruent condition] and SES 2 = [RTs for the Incongruent condition
585 – RTs for the Congruent condition]. The significance of the SES was tested with a two-tailed t-test
586 against 0. The normality of the SES was tested with the Kolmogorov-Smirnov Test (K-S).

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	Gaze		Arrow	
	SES 1	SES 2	SES 1	SES 2
	Neutral - Congruent	Incongruent-Congruent	Neutral-Congruent	Incongruent-Congruent
Effect Size in ms Mean±SD	54±47	13±36	53±54	36±62
t-test	t ₂₅ =5.78; p<0.001	t ₂₅ =1.84; p=0.07	t ₂₅ =4.97; p<0.001	t ₂₅ =2.92; p=0.007
K-S	d=0.11; ns	d=0.10; ns	d=0.12; ns	d=0.09; ns

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590 **Table 5.** Patients' percentage of correct responses in each field (left/right), for each cue (Gaze/Arrow)
591 and in the neutral condition.

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% Correct responses	Left field		Right field	
	Neutral	Congruent	Neutral	Congruent
Case				

	Gaze		Arrow		Gaze		Arrow	
GA	10	45	50	95	95	95	95	95
TJ	25	25	30	100	95	95	100	100
RM	95	100	100	90	90	90	85	85
BR	60	70	85	90	95	95	90	90
VP	60	85	80	75	80	80	95	95
BMC	70	100	100	100	100	100	100	100
KF	95	85	90	100	95	95	100	100
LC	55	95	80	90	95	95	100	100
LJ	100	100	100	100	100	100	100	100
MMT	100	95	90	100	100	100	100	100
SD	100	100	100	100	100	100	100	100
DCJ	100	100	100	100	100	100	100	100
DMC	95	95	95	75	80	80	85	85

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595 **Table 6.** Patients' profile in each field (left/right) and for each cue (Gaze/Arrow). Only patients
596 showing a z-score>0 in both sequences were identified as responders (1) (all others were identified as
597 non-responders; 0). N/A indicates patients who were unable to perform the task in the condition used
598 to compute the z-score (%CR<50%).

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	Left field		Right field	
Case	Gaze	Arrow	Gaze	Arrow
GA	N/A	N/A	1	1
TJ	N/A	N/A	0	0

RM	1	1	0	600
BR	1	1	1	601
VP	1	1	0	602
BMC	1	1	1	603
KF	1	0	0	604
LC	1	0	1	605
LJ	1	0	0	606
MMT	0	1	0	607
SD	0	0	0	608
DCJ	0	0	0	609
DMC	0	0	0	0
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Figure 1. Time course of the experimental trials. Time course for one trial of the Neutral condition (upper part), one congruent trial of the Gaze condition (middle part) and one incongruent trial of the Arrow condition (bottom part). Participants were asked to maintain their attention on the screen's center until the target appeared. When the target appeared, they were free to initiate eye movements. The experimenter was present in the room and ensured participants followed these instructions.

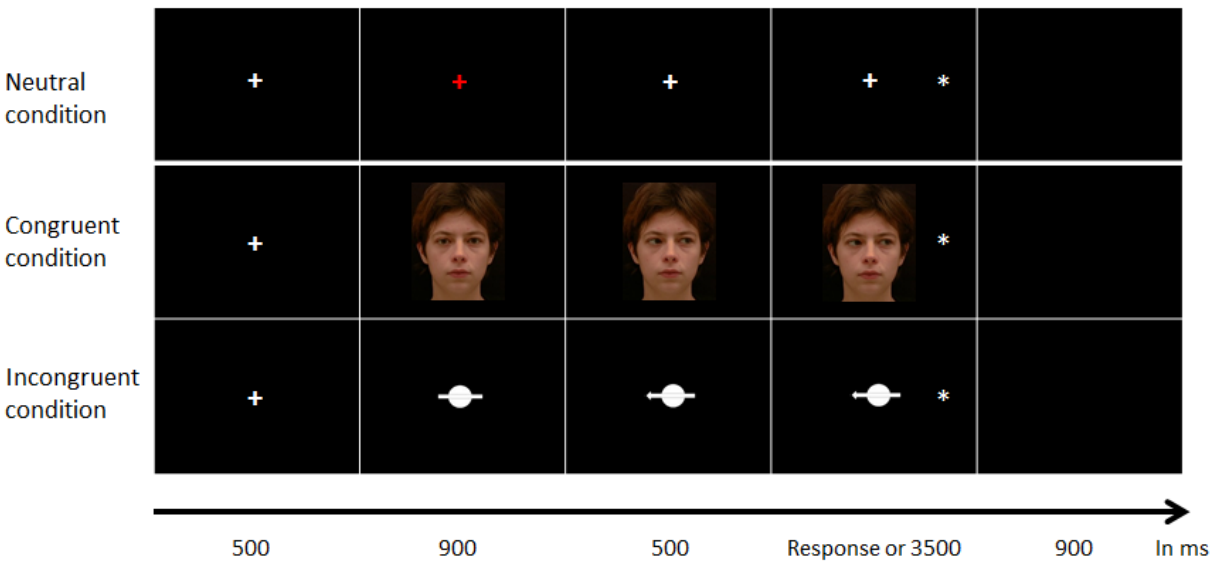
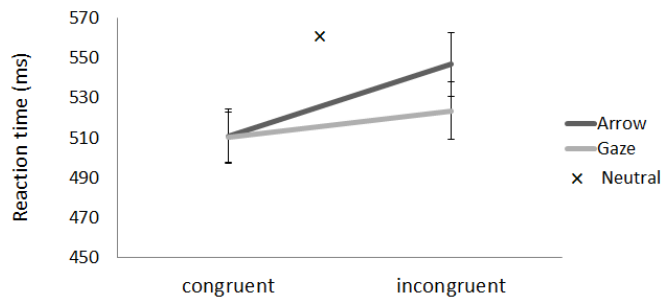


Figure 2. Reaction times. A) Reaction time for the control group (averaged over both fields) for each cue direction (congruent and incongruent) B) Reaction time for the patients in the left field (graphic on bottom left) and in the right field (graphic on bottom right) for each cue direction (congruent and incongruent). Gaze conditions are depicted with black lines, Arrow conditions with grey lines and Neutral condition with crosses. For the graphic on bottom right, the two lines (gaze and arrow conditions) overlap each other.

A) Controls



B) Patients

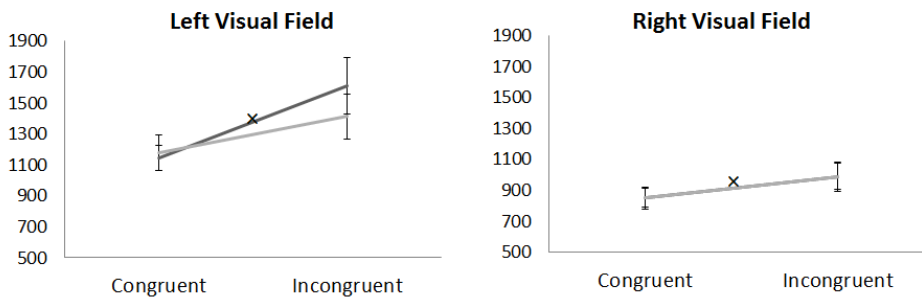
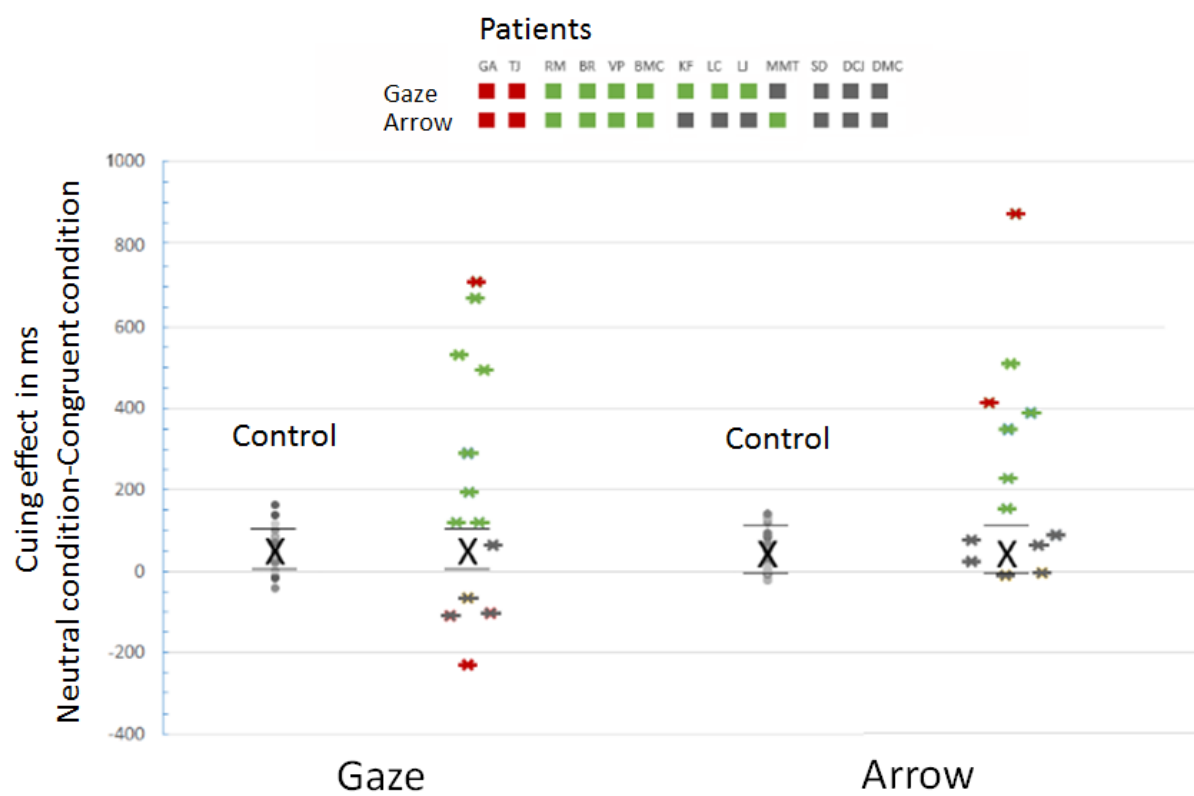


Figure 3. Individual cueing effects. Individual cueing effects (SES 1 = Neutral-Congruent Condition) for Gaze (left) and Arrow (right). Individual effects for the control participants are depicted in grey. Group means are indicated with a cross and standard deviations with horizontal bars. Individual effects for the patients with USN in the neglected (left) field are depicted in colors. Individual effects are compared to the means and SDs of the control group. Patients depicted in red were excluded from z-score analyses. Patients depicted in grey were identified as non-responders while patients depicted in green were identified as responders. Thus, the legend above the figure indicates whether each patient was a Gaze and/or Arrow responder.



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