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HAL Authorization

1 **Diagnosing Gaze and Arrow Cueing Effects in Unilateral Spatial**
2 **Neglect**

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27 study.

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

48

49

50 **1. Introduction**

51 Unilateral spatial neglect (USN) involves a difficulty to detect, respond to or orient one's
52 attention toward stimuli presented to (or represented on) the contralateral side of a brain
53 lesion, which is usually located in the right hemisphere (Heilman, Watson, & Valenstein,
54 1993). Clinical forms of USN are very heterogeneous (Vuilleumier and Saj, 2014). Yet, one
55 major characteristic of USN is that patients present difficulties in “consciously” and/or
56 “unconsciously” orienting attention to the left space (Corbetta & Shulman, 2011). Since
57 attention plays a major role in perception and cognition, allowing one to search for, detect and
58 learn about relevant sensory stimuli, USN hampers individuals' ability to recover their
59 autonomy (Bowen, Hazelton, Pollock, & Lincoln, 2013). To reduce USN, several
60 rehabilitation techniques have been proposed (Luauté, Halligan, Rossetti, Rode & Boisson,
61 2006). However, in a Cochrane review, Bowen et al. (2013) highlighted the limited effect of
62 these techniques for daily activities and the need to rely on patients' preserved abilities in
63 future rehabilitation methods.

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

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

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

92 In recent decades, numerous neuroimaging studies have demonstrated that spatial orienting is
93 implemented in bilateral networks involving parietal, temporal and frontal cortical regions, as
94 well as subcortical structures such as thalamus, superior colliculus and basal ganglia (He,
95 Shulman, Snyder & Corbetta, 2007; Ringman, Saver, Woolson, Clarke, & Adams, 2004),
96 with a stronger specialization of the right hemisphere (Bartolomeo, Thiebaut de Schotten, &
97 Chica, 2012; Corbetta & Shulman, 2011; He et al, 2007). Theoretically, a lesion in those large
98 right networks may cause USN (Ringman et al, 2004). Meta-analyses confirm that cortical
99 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

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

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

138 **2. Methods**

139 ***2.1. Participants***

140 A total of 39 right-handed native French-speaking participants were included in the study: 13
141 patients with a diagnosed left USN secondary to right brain damage (9 females, mean age =
142 64.7 years \pm 9.6) and 26 healthy control elderly participants (16 females; mean age=66.4 years
143 \pm 10.0)¹. The patients with left USN were recruited from the neurological rehabilitation unit of
144 "Centre de reeducation et de réadaptation fonctionnelles Le Bourbonnais UGECAM BFC" at
145 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).

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

151 **(Table 1 about here)**

152 **(Table 2 about here)**

153 ***2.2. Stimuli***

154 *2.2.1. Gaze cues*

155 Face stimuli consisted of 40 static color photographs of 20 individuals (10 males/10 females)
156 selected from a database of digitized portraits of adult faces (see Conty, N'Diaye, Tijus, &
157 George, 2007). All faces were of individuals unknown to our participants and had a neutral
158 expression. Head direction was always oriented straight toward the observer. Each individual
159 was presented in two different views: one with the eyes directed straight toward the observer
160 (Direct Gaze), and one with the eyes averted 30° toward the right side of the observer's
161 position (Averted Gaze). To avoid any unintended differences in picture backgrounds, the eye
162 region in the averted gaze stimuli was cut and pasted into the very same position within the
163 photographs used for the direct gaze stimuli. Next, for all stimuli (including Direct Gaze
164 faces), left sides were obtained by mirror-imaging. All stimuli were presented in 256 colors
165 and reduced to a height of 310 pixels and a width of 148 pixels while preserving their
166 proportion. During the experiment, the face stimuli covered a visual angle of approximately
167 7.5° vertically and 6° horizontally.

168 *2.2.2. Arrow cues*

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

174 2.2.3. *Target*

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

177 2.3. *Procedure*

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

183 The experiment was divided into two 100-trial sequences with a break after 50 trials. We used
184 3 main conditions: Gaze (40 trials per sequence), Arrow (40 trials per sequence) and Neutral
185 (20 trials per sequence). In each sequence, trial presentation was randomized across
186 participants. Each trial started with a 500 ms presentation of a fixation cross located at the
187 level of the stimulus face's eyes (in the Gaze condition) and bar (in the Arrow condition).
188 Then, a face with a direct gaze (or the bar) appeared on the screen. After 900ms, the face was
189 replaced by the same face gazing to the right (in half of the trials) or to the left. Thus, in the
190 Gaze condition, participants viewed a face in which the eyes moved away from him/her. In
191 the Arrow condition, the bar was replaced by the arrow pointing to the right (in half of the
192 trials) or to the left. In the Neutral condition, the fixation cross remained on the screen during

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

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

204 **(Figure 1 about here)**

205 ***2.4. Statistical analyses***

206 *2.4.1. Group analysis*

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

214 *2.4.2. Standard effect sizes of the control group*

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

220 *2.4.3. Individual patient analysis*

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

230 *2.4.4. Correlation analyses*

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

235 *2.4.5. Regression analyses*

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

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

244 **3. Results**

245 *3.1. Group Analysis*

246 *3.1.1. Control group*

247 The ANOVA run on RTs showed a main effect of Cue Direction ($F(1,25)=10.59$; $p<0.01$).
248 Control participants were faster on Congruent (mean RTs = 510 ± 17) versus Incongruent trials
249 (mean RTs = 535 ± 19). No other effects or interactions were observed. The ANOVA run on
250 %CR revealed no main effects or interactions. Control participants performed well on all
251 conditions (mean %CR = 99 ± 0.5).

252 *3.1.2. Patients*

253 The RT analyses showed a main effect of Field ($F(1,12)=20.91$; $p<0.001$). Patients were faster
254 at detecting the target when it appeared on the right (mean RTs= 920 ± 73) versus the left
255 (mean RTs= 1339 ± 111). We also observed a main effect of Cue Direction ($F(1,12)=8.80$;
256 $p=0.011$). Patients were faster for Congruent (mean RTs= 1008 ± 67) versus Incongruent trials
257 (mean RTs= 1251 ± 111). Importantly, there was an interaction between Field and Cue
258 ($F(1,12)=6.38$; $p=0.026$). Post-hoc analyses showed that the effect of Cue Direction was
259 greater in the left field ($p<.0001$; mean effect size= 322 ± 112) than in the right ($p=0.04$; mean
260 effect size= 135 ± 46). No other main effects or interactions were observed for RTs.

261 The ANOVA run on %CR showed a main effect of Field ($F(1,12)= 5.29$; $p=0.04$). Patients
262 performed better in the right field (mean %CR = 94 ± 1) than the left (mean %CR = 79 ± 6). Cue
263 Direction failed to reach significance ($F(1,12)=3.91$; $p=0.07$). However, the interaction
264 between Field and Cue Direction reached significance ($F(1,12)=5.32$; $p=0.04$). Post-hoc
265 analyses revealed that patients performed better on Congruent than Incongruent trials but only
266 in the left field ($p<0.003$ – effect size= $10\%\pm 5$).

267 **(Table 3 about here)**

268

269 **(Figure 2 about here)**

270 ***3.2. Standard effect sizes in the control group***

271 We then computed standard effect sizes (SES) of Gaze and Arrow cueing (see analyses). For
272 each cue, we tested the normality and the significance of each SES: SES 1 = [RTs for the
273 Neutral condition – RTs for the Congruent condition] and SES 2 = [RTs for the Incongruent
274 condition – RTs for the Congruent condition]. The analyses revealed that SES 1 did not
275 diverge from a Gaussian distribution and differed significantly from 0 for both Gaze and
276 Arrow (see Table 4 for details). SES 2 did not diverge from a Gaussian distribution either, but
277 failed to reach significance for Gaze (see Table 4 for details). Further analyses revealed that
278 SES 1 was larger than SES 2 for Gaze ($t=3.91$; $p<0.01$) but not for Arrow ($p=.16$). Altogether,
279 these results revealed that SES 1 was a more relevant standard of the cueing effects than SES
280 2 (especially for Gaze).

281 **(Table 4 about here)**

282 ***3.3. Individual patient analyses***

283 Usually, z values below -1.65 or above +1.65 are considered to deviate significantly from the
284 normal score. This method allows researchers to test for a deficit in the single case. Here,
285 however, the purpose is not to test for a deficit, but for the presence of an effect. A z-score of
286 0 corresponds to the mean cueing effect observed in the control group, which significantly
287 differed from 0. In others words, $z > 0$ indicates the presence of a cueing effect. We thus
288 applied a cut-off of $z > 0$ to determine the presence of cueing effects.

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

300 **(Table 5 about here)**

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

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

308 **(Table 6 about here)**

309
310 **(Figure 3 about here)**

311 312 *3.4. Correlations and regression analyses*

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

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

320 **4. Discussion**

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

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

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

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

346 The analyses run at the individual level confirm this hypothesis. We computed standard gaze
347 and arrow cueing effects (RTs for the Neutral condition – RTs for the Congruent condition)
348 from the control group. The patients' cueing effects were also computed and converted to z -
349 scores based on the control group's means and SDs. Using a cut-off of $z > 0$ at the individual
350 scale, we identified, in the left field, 3 responders to Gaze only, 1 responder to Arrows only, 4
351 Gaze and Arrow responders, and 3 Non-responders (for a total of 11 patients whose
352 performance in the left field allowed z -score computation). The low rate of left Non-
353 responders observed in this study strengthens the view that gaze and/or arrow cueing effects
354 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

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

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

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

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

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

421 **5. Conclusions**

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

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547 **Tables and figures**

548 **Table 1. Patient characteristics.** Left USN diagnosis was based on clinical observation, lesion localization, and behavioral and neuropsychological tests (see
549 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
550 psychiatric disorders. Patients underwent a neuropsychological evaluation testing episodic memory with the RL/RI-16 items (Van Der Linden et al, 2004),
551 executive functions with the Grefex Battery (Godefroy, 2008), attentional functions with the TAP (Zimmermann & Fimm, 2010) and instrumental functions
552 with the VOSP Test, visuo-constructive reproduction and DO80 (Deloche & Hannequin, 1997). Neglect symptoms were tested with the Bell Test, the line
553 bisection and the Ogden scene from “Batterie d’Evaluation de la Négligence Unilatérale du Geren” (BEN, Azouvi et al, 2002). Moreover, we used two
554 subtests from the TAP (Zimmermann & Fimm, 2010) to further support the diagnosis: visual field examination and examination of visual field “neglect
555 condition”. Sex (F = female; M = male); Laterality (R = right-handed; Amb = ambidextrous); Etiology (TBI = traumatic brain injury); Isch = ischemia; Hem =
556 hemorrhage; MD: motor deficit (0 = absent; 1 = monoparesis; 2 = incomplete hemiparesis; 3 = complete); SD: somatosensory deficit (0 = absent; 1 =
557 superficial; 2 = incomplete superficial and deep; 3 = complete); LHH: left homonymous hemianopia (A = absent; P = present; NE: not analyzable); L-F bell’s
558 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
559 omissions on the right); Line Bisection deviation in millimeters (positive value = deviation toward the right; negative value = deviation toward the left); Visual
560 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
561 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
562 “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
563 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
564 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*

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

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	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

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577 **Table 3.** Percentage of correct responses and standard error (SE) for the control group (upper part) and
 578 the patients with USN (bottom part) on all experimental conditions. Control participants performed at
 579 ceiling on all conditions. Patients performed better in the right field, and their performance in the left
 580 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).

587

	Gaze		Arrow	
	SES 1 Neutral - Congruent	SES 2 Incongruent-Congruent	SES 1 Neutral-Congruent	SES 2 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.

592

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

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

599

Case	Left field		Right field	
	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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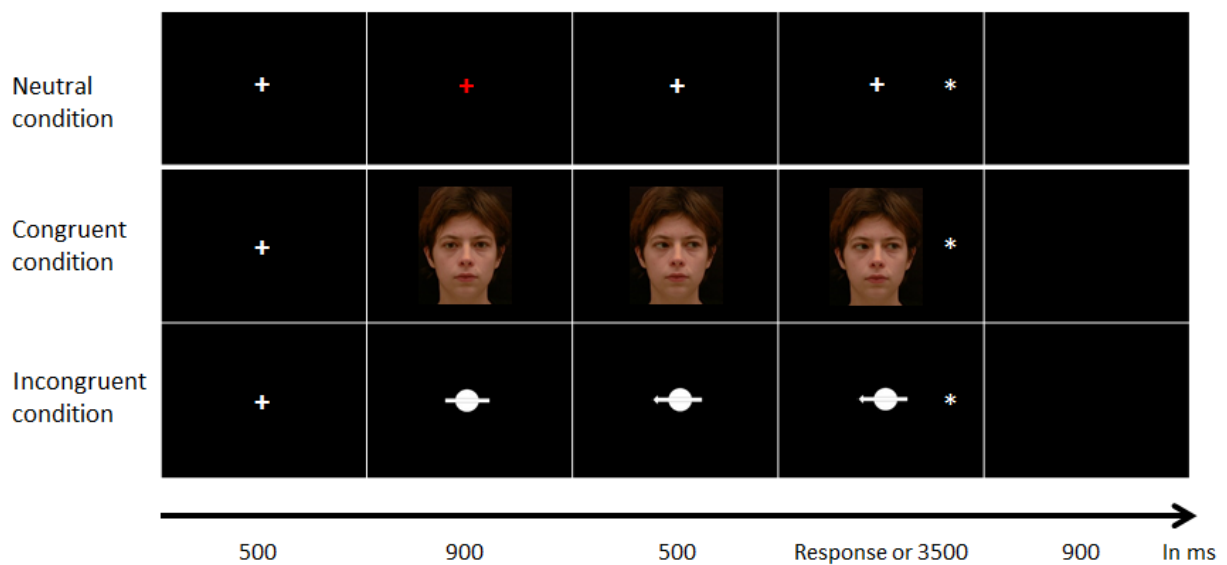
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615 **Figure 1. Time course of the experimental trials.** Time course for one trial of the Neutral condition
 616 (upper part), one congruent trial of the Gaze condition (middle part) and one incongruent trial of the
 617 Arrow condition (bottom part). Participants were asked to maintain their attention on the screen's
 618 center until the target appeared. When the target appeared, they were free to initiate eye movements.
 619 The experimenter was present in the room and ensured participants followed these instructions.
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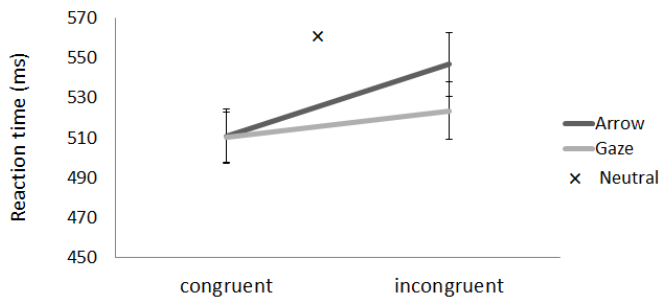
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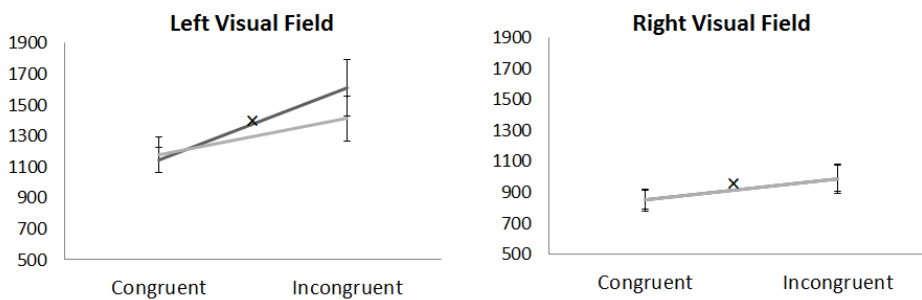
624 **Figure 2. Reaction times.** A) Reaction time for the control group (averaged over both fields) for each
 625 cue direction (congruent and incongruent) B) Reaction time for the patients in the left field (graphic on
 626 bottom left) and in the right field (graphic on bottom right) for each cue direction (congruent and
 627 incongruent). Gaze conditions are depicted with black lines, Arrow conditions with grey lines and
 628 Neutral condition with crosses. For the graphic on bottom right, the two lines (gaze and arrow
 629 conditions) overlap each other.

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A) Controls



B) Patients

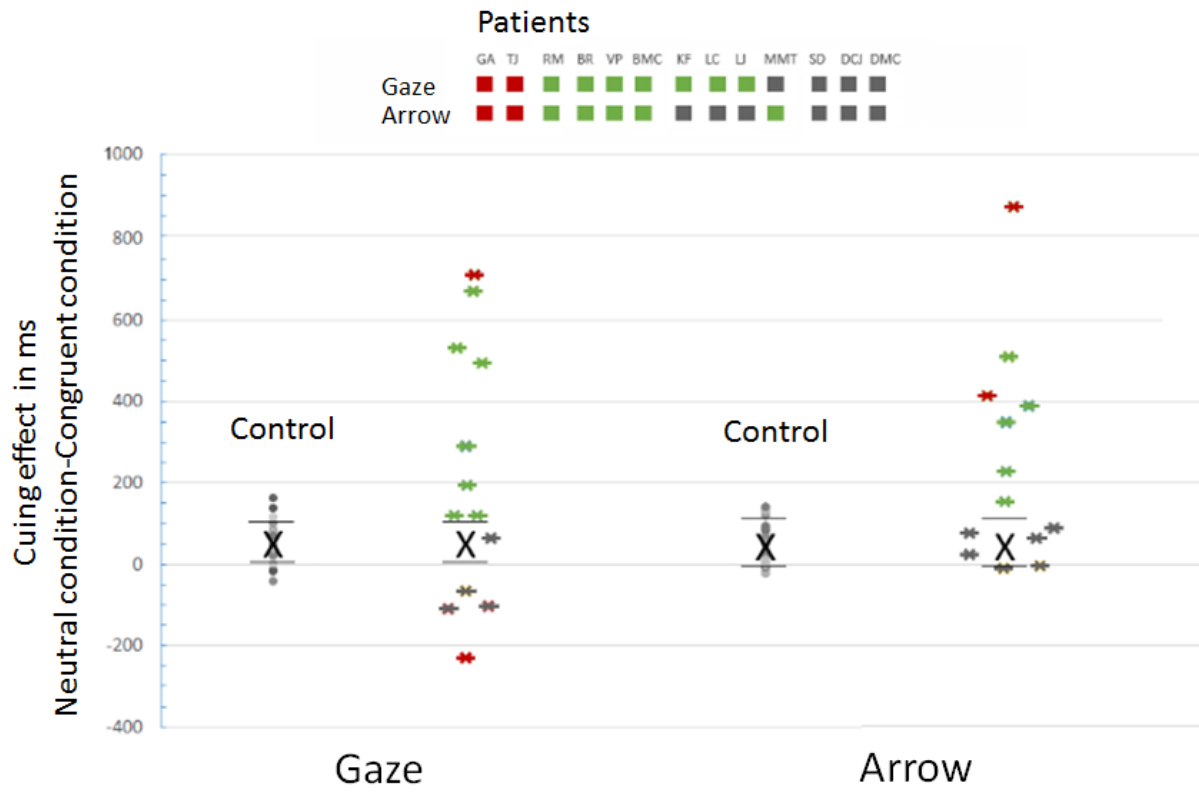


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634 **Figure 3. Individual cueing effects.** Individual cueing effects (SES 1 = Neutral-Congruent Condition)
 635 for Gaze (left) and Arrow (right). Individual effects for the control participants are depicted in grey.
 636 Group means are indicated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



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