Multisensory integration in Hemianopia and Unilateral Spatial Neglect: Evidence from the Sound Induced Flash Illusion

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ABSTRACT

Recent neuropsychological evidence suggests that acquired brain lesions can, in some instances, abolish the ability to integrate inputs from different sensory modalities, disrupting multisensory perception. We explored the ability to perceive multisensory events, in particular the integrity of audio-visual processing in the temporal domain, in brain-damaged patients with visual field defects (VFD), or with unilateral spatial neglect (USN), by assessing their sensitivity to the 'Sound-Induced Flash Illusion' (SIFI). The study yielded two key findings. Firstly, the 'fission' illusion (namely, seeing multiple flashes when a single flash is paired with multiple sounds) is reduced in left- and right-brain-damaged patients with VFD, but not in right-brain-damaged patients with left USN. The disruption of the fission illusion is proportional to the extent of the occipital damage. Secondly, a reliable 'fusion' illusion (namely, seeing less flashes when a single sound is paired with multiple flashes) is evoked in USN patients, but neither in VFD patients, nor in healthy age-matched control participants. A control experiment showed that the fusion, but not the fission, illusion is lost in older (>50 year-old), as compared with younger healthy participants (<30 year-old). This evidence indicates that the fission and fusion illusions are dissociable multisensory phenomena, altered differently by impairments of visual perception (i.e. VFD) and spatial attention (i.e. USN). The occipital cortex represents a key cortical site for binding auditory and visual stimuli in the SIFI, while damage to right-hemisphere areas mediating spatial attention and awareness does not prevent the integration of audio-visual inputs in the temporal domain.

Keywords: multisensory perception, visual field defect, neglect, temporal processing, sound-induced flash illusion

1. INTRODUCTION

Crossmodal illusions can result from the integration of discordant information from different sensory modalities. These illusions represent perceptual strategies for dealing with inter-sensory conflicts, yielding coherent to incoherent perceptual experiences across sensory systems (Bolognini et al., 2015a). Recent studies indicate that the perception of crossmodal illusions can be selectively altered in brain-damaged patients, depending on their neuropychological disorder (reviews in Bolognini et al., 2013a, 2015a). This is, for instance, the case of the ventriloquist illusion (Howard and Templeton, 1966), whereby the perceived location of a sound is captured by the location of a synchronous, but spatially disparate, visual stimulus (Thurlow and Jack, 1973; Welch and Warren, 1980; Warren et al., 1981). The ventriloquist illusion is disrupted in patients with homonymous Visual Field Defects (VFD), contralateral to the side of the hemispheric lesion, but is preserved in right-brain-damaged patients with left Unilateral Spatial Neglect (USN) (Bertelson et al., 2000; Leo et al., 2008; Passamonti et al., 2009). These findings suggest that the ability to integrate conflicting visual and auditory information in the spatial domain can be selectively compromised by a primary sensory visual deficit, but not by a higher-order disorder of spatial attention.

The present study went one step further, by investigating whether and how cerebral lesions impairing vision (i.e., homonymous VFD), or spatial attention (i.e., USN), impact the ability to bind audio-visual signals in the temporal domain. To explore multisensory perception in brain-damaged patients with VFD or left USN, we took advantage of a powerful crossmodal audio-visual illusion, namely the Sound-Induced Flash Illusion (SIFI) (Shams et al., 2000, 2002),

In the SIFI, two rapid tones (beeps), accompanying a single brief visual flash induce the illusory perception of seeing a double flash, an effect known as the '*fission'* illusion; by increasing the number of beeps, the number of seen flashes tends to increase. A complementary '*fusion'* illusion may also occur, whereby two, or more, flashes fuse into one, when presented along with a single beep (Andersen et al., 2004, 2005; Mishra et al., 2008; Shams et al., 2005; Watkins et al., 2006). Electrophysiological and brain imaging studies show that the neural underpinnings of the

SIFI involve a rapid interplay between the primary auditory and the primary visual areas (V1 and V2), along with a crossmodal modulatory feedback from the Superior Temporal Sulcus and the Posterior Parietal Cortex (PPC) to the visual cortex (Shams et al., 2001; Watkins et al., 2006; Mishra et al., 2007; 2010). Accordingly, the SIFI can be altered by transcranial Direct Current Stimulation (tDCS) of the occipital cortex and of the Superior Temporal Gyrus (STG) of the right hemisphere (Bolognini et al., 2011): the fission illusion is increased by anodal (excitatory) tDCS over the STG, but decreased by anodal tDCS over the occipital cortex; conversely, cathodal tDCS over the STG decreases the fission illusion, and increases it when delivered over the occipital cortex. By contrast, the fusion illusion is not modulated by either occipital or temporal (anodal and cathodal) tDCS (Bolognini et al., 2011). The link between the level of excitability of the occipital cortex and the SIFI is further supported by evidence from studies on patients with migraine. The pathophysiology of migraine involves a hyper-excitability of the occipital cortex. Accordingly, migraineurs (in particular those with aura) show a reduced fission illusion, and normal fusion illusion (Brighina et al., 2015): this is consistent with the above-discussed findings that anodal occipital tDCS decreases the fission illusion (Bolognini et al., 2011).

The role of the posterior parietal areas in the SIFI remains controversial. Neither anodal nor cathodal tDCS of the right PPC modulates the SIFI (Bolognini et al., 2011). Conversely, low frequency (1 Hz) repetitive Transcranial Magnetic Stimulation (rTMS) delivered to the angular gyrus, but not to the supramarginal gyrus, of the right inferior parietal lobule, reduces the fission illusion in neurologically healthy participants (Kamke et al., 2012; Hamilton et al., 2013).

Homonymous VFDs are brought about by damage to the retrochiasmatic visual pathways, causing blindness in the sectors of the visual field (i.e., VFD), which retinotopically correspond to the damaged tissue (Zihl and Kennard, 1996). In homonymous hemianopia, vision is lost in the entire half-field contralateral to the side of the hemispheric lesion (contralesional), whereas in homonymous quadrantanopia the visual defect is restricted to the upper or lower quadrant of the contralesional half-field. Patients with VFD may show additional non-visual deficits, such as spatial

impairments in the auditory modality (Kerkhoff et al., 1999; Lewald et al., 2009), suggesting that the primary visual deficit may affect aspects of processing in other sensory modalities.

In contrast, left USN is most frequently associated with lesions affecting the higher-order, association, fronto-temporo-parietal areas of the right hemisphere. Right-brain-damaged patients with left USN are unable to report sensory events occurring in the contralesional (left) side of space, and to explore it through motor acts; USN is currently conceived as a higher-order disorder of spatial attention and representation (Vallar and Bolognini, 2014). Whereas the core clinical symptoms and signs of VFD involve visual deficits, USN has multisensory features (see, e.g., Jacobs et al., 2012), and may involve somatosensory and auditory modalities (De Renzi et al., 1970; de Renzi, 1982; Bisiach et al., 1984; Beschin et al., 1996; Clarke and Thiran 2004; Pavani et al. 2003; Gainotti, 2010). USN-related deficits in the visual, somatosensory, and auditory modalities can occur in various combinations, suggesting that spatial cognition and awareness are based on the interaction between multiple, modality-specific, neural systems (Umiltà, 1995; Brozzoli et al., 2006; Vallar and Bolognini, 2014).

Despite the presence of modality-specific deficits, a number of multisensory abilities are preserved in brain-damaged patients with USN or with VFD (see for a review, Bolognini et al., 2013a; Vallar and Bolognini, 2014). These spared abilities for multisensory integration may even help compensating for modality-specific disorders. For example, brain-damaged patients with USN or with VFD show a higher detection rate of visual stimuli in the contralesional visual half-field, when tactile or auditory stimuli are presented at the same spatial location, and at the same time, of the visual target (e.g., Frassinetti et al, 2005; Schendel and Robertson, 2004; Leo et al., 2008). This evidence has guided the development of treatments for VFD with multisensory features, which have been shown to be more effective than the standard purely visual therapies (Bolognini et al., 2005; Passamonti et al., 2009; Keller and Lefin-Ranck, 2010; Tinelli et al., 2015).

In the light of this evidence, we investigated whether brain-damaged patients with left USN and brain-damaged patients with VFD (without USN) experience the SIFI, as compared to healthy

participants. We aimed at exploring whether a cerebral lesion bringing about a primary sensory deficit in the visual modality (VFD), or an impairment of visuo-spatial attention (USN), can alter multisensory capabilities, as indexed by the fission and fusion illusions. This, in turn, allows investigating whether lesions affecting the primary visual cortex (in patients with VFD) and higher-level association areas (in patients with USN) may disrupt the fission and fusion illusions.

2. MATERIALS AND METHODS

2.1. Participants

Thirty-one right-handed participants took part in the experiment, which was conducted at the Neuropsychological Laboratory of the IRCCS Istituto Auxologico Italiano (Milan, Italy). All participants had normal hearing, no history of hearing disorders, and normal or corrected-to-normal vision. Participants were naïve as to the purpose of the experiment and provided written informed consent to the protocol. The study was approved by the Ethical Committee of the Hospital, and carried out in accordance with the ethical standards of the Declaration of Helsinki (BMJ 1991; 302:1194). Three groups of participants entered the study.

1) Twelve neurologically unimpaired individuals (5 males; mean age = 65.41, Standard Deviation ± 9.17 years, range = 50-82; mean years of schooling = 9.83 ± 3.83, range = 5-18), without history or evidence of neurological or psychiatric diseases, served as control participants.

2) Eleven brain-damaged patients had homonymous VFD (9 males; mean age = 50.5 ± 14.49 years, range = 25-69; mean years of schooling = 11.7 ± 5.16, range = 5-18). Patients had suffered a cerebral ischemic or hemorrhagic stroke. Seven patients had a left-hemispheric lesion (6 with a right-sided homonymous hemianopia, 1 with a right-sided quadrantanopia), 4 patients had a right-hemispheric lesion (2 with a left-sided homonymous hemianopia, 2 with a left-sided quadrantanopia). The visual field loss was assessed by a standard Humphrey visual field perimetry. Patients were tested in a chronic stage after stroke (duration of disease = 14.68 ± 10.6 months, range = 3-37 months), when visual sensitivity is stable (Zhang et al., 2006).

3) Eight right-brain-damaged patients showed left USN (6 males; mean age = 71.25 ± 9.28 years, range = 51-83; mean years of schooling = 11.37 ± 4.13, range = 5-18). Seven patients had suffered a cerebrovascular disease and were tested in a chronic stage of illness (duration of disease= 4.40 ± 4.1 months, range= 1.5-12 months). One patient had a surgically removed parasellar meningioma.

Every brain-damaged patient underwent a neuropsychological assessment of USN prior to the experiment, comprising a battery of standardized tests, as described below. All participants had normal or corrected-to-normal visual acuity. Brain-damaged patients were fully oriented in time and space, and they had neither history nor evidence of previous neurological and psychiatric disorders. The demographic and clinical characteristics of the brain-damaged patients are summarized in Table 1.

[Table 1 about here]

2.2. Neuropsychological assessment

One week before the experimental session, all patients underwent a standard neurological examination for the assessment of contralesional motor, somatosensory, and visual half-field deficits. The motor examination of the upper and lower limbs included the assessment of asymmetric strength deficits, while visual and tactile deficits, including extinction to bilateral stimuli, were assessed by manual confrontation (Bisiach and Faglioni, 1974). In both the tactile and the visual tests, the patients were warned that the stimulation could be delivered on the left or the right side (unilateral), or on both sides simultaneously (bilateral); stimuli were administered in two series: a first series with 5 unilateral left-sided, 5 unilateral right-sided and 10 bilateral simultaneous stimuli, in a random fixed order; a second series with 10 unilateral left-sided and 10 unilateral right-sided stimuli, in a random fixed order. At this standard neurological exam, the presence of a visual-field deficit is indexed by the lack of report of ≥30% of contralesional single stimuli; the presence

of extinction is indexed by the lack of report of ≥30% of contralesional visual stimuli under conditions of double simultaneous stimulation, associated with a correct report of ≥80% of single contralesional stimuli (Bisiach and Faglioni, 1974; Bisiach et al. 1983).

The battery of tests for the assessment of USN (for details see, Bolognini et al., 2011; Fortis et al., 2010) included:

- *Cancellation tasks: Letter* (Diller and Weinberg, 1977), *Star* (Wilson et al., 1987), and *Bell* (Gauthier et al., 1989) target cancellation. Patients received instructions to cross out all of the targets, intermingled with distracters, printed on a paper sheet, whose centre was aligned with the mid-sagittal plane of the patient's trunk. In healthy participants the maximum difference between omission errors in the two sides of the sheet was 2 targets for the Letter, 4 targets for the Bell, and 1 target for the Star cancellation task (Vallar et al., 1994).

- *Line bisection.* The patient was required to mark with a pencil the midpoint of 6 horizontal black lines (2 lines, each 2 mm in width, of the following lengths: 10, 15, and 25 cm), presented in a random fixed order. Each line was printed centrally on an A4 sheet. For scoring, the length of each bisected line, namely, from the left end of the line to the participant's mark, was measured to the nearest mm, and then converted into a standardized score (percent deviation), using the following formula: measured left half *minus* objective half/ objective half x 100 (Rode et al., 2006). This score yielded positive values for rightward deviations, negative values for leftward deviations. A deviation score towards the side of the hemispheric lesion (leftward deviation for left-brain-damaged-patients, rightward deviation for right-brain-damaged patients was considered as indicative of USN (Vallar and Bolognini, 2014). The mean percentage deviation score of 65 neurologically unimpaired participants was -1.21% (±3.48) (Fortis et al., 2010).

- *Five-element Complex Drawing* (Gainotti et al., 1972) assessed the participants' ability to copy a complex figure consisting of 5 elements (from left to right: 2 trees, 1 house, and 2 pine

trees). The total score ranged from 0 to 10. A score lower than 10 indicated a defective performance (Fortis et al., 2010).

Patients used their unaffected hand, ipsilateral to the damaged hemisphere, to perform the tasks; in all tasks, the centre of the sheet was aligned with the mid-sagittal plane of the patient's trunk.

Table 1 shows the individual scores of all brain-damaged patients at the baseline evaluation. The presence of USN was determined on the basis of a pattern of defective performance, in at least 2 out of the 5 tests administered for assessing the deficit, namely: in cancellation and drawing tasks, omissions contralateral to the side of the hemispheric lesion (contralesional; in right-brain-damaged patients, left-sided omission errors); in line bisection, a deviation of the subjective midpoint on the same side of the hemispheric lesion (ipsilesional; in right-brain-damaged patients, a rightward deviation). Accordingly to this criterion, VFD patients did not show comorbidity with USN (see Table 1).

2.3. Lesion data

Lesions of the 19 brain-damaged patients enrolled in the study were assessed by CT scans in 12 patients, and by MRI scans in 7 patients. Regions of Interest (ROIs) defined the location and the size of the lesion for each patient. These were reconstructed by means of a template technique, by manually drawing the lesion on the standard template from the Montreal Neurological Institute (Rorden and Brett, 2000), on each 2D slice of a 3D volume. Figure 1 shows the overlay lesion plot of patients with VFD without USN, and of right-brain-damaged patients with left USN. Mean lesion volumes were 113.88 (±125.85 cc^3, range = 4.2–342.7 cc^3) in right-brain-damaged patients with left USN, and 25.24 (± 19.96 cc^3, range = 1.2–58.1 cc3) in patients with VFD without USN. As shown in Figure 1, right-brain-damaged patients with left USN had larger lesions, involving the frontal lobe in 6 patients (mean voxels affected by the lesion= 30170 ± 28604), the parietal lobe in 3 patients (26167 ± 16627 voxels), and the temporal lobe in 4 patients (25392 ± 28854 voxels); the

occipital lobe was damaged in two right-brain-damaged patients with left USN (namely, P17= 7495 voxels, P19= 5487 voxels). Conversely, all patients with VFD without USN had a lesion involving the occipital lobe (10333 ± 12642 voxels), and extending to the temporal lobe in 8 patients (7097 ± 8484 voxels), and to the parietal lobe in 3 patients (3592 ± 6095 voxels); the frontal lobe was spared in all patients with VFD.

[Figure 1 about here]

2.4. SIFI: Stimuli and procedure

The SIFI was designed and implemented using the same stimuli, and procedures, as in the original study (Shams et al., 2000; see also Bolognini et al., 2011, 2013b).

Participants sat in front of a CRT computer monitor (≈57 cm away; Fujitsu Siemens B796-1: resolution 1024 × 768, refresh rate 75 Hz). They gazed at a white fixation cross, which was displayed at the beginning of each trial in the centre of a black screen (luminance: 0.02 cd/m^2). Participants were required to fixate the white cross for the entire duration of the trial. The visual stimulus consisted of a white disk of 2° diameter, presented 5° below the fixation cross, which could be flashed from 1 to 4 times. Single and multiple flashes could be presented alone or accompanied with 0–4 beeps. The participant's task was to report verbally the number of seen flashes.

Auditory tones were presented through a set of external speakers, located beside the screen and aligned with the flashes. The duration of each flash (luminance: 118 cd/m^2), and of each auditory stimulus (80 dB SPL tone, frequency of 3.5 kHz), was set to one refresh period of the monitor (≈ 13 msec). The inter-flash interval was of 65 msec, while the inter-tone interval was of 52 msec. In the crossmodal conditions, the first flash was always preceded by the first beep by 26 msec. Visual and auditory parameters, as well as inter-stimulus intervals (ISI), were selected with

reference to previous studies, showing that the likelihood of induction of the SIFI is maximized under these conditions (Shams and Kim, 2010).

Participants were presented with 11 stimulus combinations (F = flash stimulus; B = beep stimulus): fission trials (F1B0, F1B1, F1B2, F1B3, F1B4), and fusion trials (F2B0, F2B1, F3B0, F3B1, F4B0, F4B1). Each condition was repeated, in random order, 10 times, for a total of 110 trials, lasting for ≈10 min. At the beginning of each session, 11 practice trials were administered, but not included in the subsequent analyses. In this training session, we also checked the participant's ability of correctly counting the number of sounds and flashes. Stimulus presentation, timing and response recording were under computer control (E-prime Software, Psychology Software Tools, Pittsburgh, PA).

2.5. Statistical Analyses

Statistical analyses were performed using the Statistica Software (Statsoft, Version 6.0, StatSoft Italia SRL). In order to assess the presence of the fission and fusion illusions in the three experimental groups, two repeated-measures Analyses of Variance (ANOVA), one for each illusory effect, were performed. For the fission illusion, the participants' mean responses (number of seen flashes) to 1 flash (F) trials (combined with 0-4 beeps, B) were submitted to a 2-way ANOVA, with the 5-level *Beep* as the within-subject main factor, and the 3-level *Group* (Control, VFD, USN) as the between-subjects main factor. For the fusion illusion, the mean number of seen flashes was analyzed with a 3-way ANOVA, with *Beep* (B, 0-1) and *Flash* (F, 2-4) as the within-subject main factors, and *Group* as the between-subjects main factor (Control, VFD, USN).

Omission errors, namely trials where patients failed in seeing any flash, never exceeded 3% of responses and were excluded from analyses.

The same ANOVA's models were used in order to assess hemispheric asymmetries in the illusory effects in the VFD patients, by comparing the scores of patients with right-sided VFD (N= 4), due to a left hemispheric lesion, with those of patients with left-sided VFD (N= 7), due to a right

hemispheric lesion. Hence, these patients' scores were submitted to 2 ANOVAs, 1 for each illusory effect, which now included also *Half-field* (2 levels: left-VFD and right-VFD), as the between-subjects factor, and the within-subjects factors *Beep* for the fission illusion, and *Beep* and *Flash* for the fusion illusion.

For each data set, the assumption of sphericity was assessed by Mauchly's test, with violations being adjusted by the Greenhouse–Geisser correction. For significant main effects and interactions, post-hoc multiple comparisons were performed with the Bonferroni test. Effect sizes in the ANOVAs were assessed by calculating the partial Eta Squared ($p\eta^2$).

2.6. Results

2.6.1. Fission Illusion

Figure 2A shows that both healthy controls and VFD patients exhibited the fission illusion, reporting a greater number of flashes when a single flash was associated to more than one beep, with an increase of the number of reported flashes as the number of beeps increased. Importantly, VFD patients were less sensitive to the fission illusion, reporting fewer flashes in the crossmodal illusory trials than healthy controls and USN patients. The ANOVA showed significant main effects of *Beep* ($F_{4,112} = 114.46$, $P < 0.0001$, $p\eta^2 = 0.80$), and *Group* ($F_{2,28} = 10.38$, $P = 0.0004$, $p\eta^2 = 0.43$). The *Group* by *Beep* interaction was significant ($F_{8,112} = 3.86$, $P = 0.001$, $p\eta^2 = 0.32$). Post-hoc comparisons showed an increased number of seen flashes in all illusory, multiple-beep trials, as compared to the one-flash trials, in both healthy controls (F1B0 = 1.16 and F1B1 = 1.25 *vs*. F1B2 = 1.97, F1B3= 2.48, F1B4 = 2.59, all *Ps* < 0.01), and in USN patients (F1B0 = 1.41 and F1B1 = 1.20 *vs*. F1B2 = 2.00, F1B3= 2.43, F1B4 = 2.59, all *Ps* < 0.001), indexing a reliable fission illusion. Instead, in VFD patients, the fission illusion emerged only when more than two beeps were combined with one flash (F1B0 = 1.13 and F1B1 = 1.11 *vs.* F1B2 = 1.44, *P* = 0.9, *vs.* F1B3= 1.82 and F1B4 = 1.90, *Ps* < 0.001).

The significant *Group* by *Beep* interaction was further explored by 5 one-way ANOVAs, comparing the 3 groups (Control, VFD, USN) in each stimulus condition. No differences among the three groups were found for the non-illusory trials, namely F1B0 ($F_{2,28}$ = 3.13, *P* = 0.06, $p\eta^2$ = 0.15), and F1B1 ($F_{2,28}$ = 0.80, *P* = 0.5, $p\eta^2$ = 0.05). However, for the critical illusory conditions, the performance of the 3 groups was significantly different: F1B2 ($F_{2,28}$ = 18.39, *P* = 0.0001, $p\eta^2$ = 0.57), F1B3 ($F_{2,28}$ = 8.19, *P* = 0.002, $p\eta^2$ = 0.37), and F1B4 ($F_{2,28}$ = 6.63, *P* = 0.004, $p\eta^2$ = 0.32). Post-hoc comparisons showed that, for every illusory condition, VFD patients always reported fewer flashes, as compared to both controls and USN patients (all *P*s < 0.01). Instead, USN patients and controls did not differ from each other in any illusory condition (all *P*s > 0.9).

The ANOVA with the between-subjects factor *Half-field*, and the within-subjects factor *Beep* showed that a significant main effect of *Beep* ($F_{4,36}$ = 39.37, *P* < 0.0001, $p\eta^2$ = 0.81), while the main effect of *Half-field* ($F_{1,9}$ = 0.03, *P* = 0.9, $p\eta^2$ = 0.01) and the *Half-field* by *Beep* interaction ($F_{4,36}$ = 0.69, *P* = 0.6, $p\eta^2$ = 0.07) did not attain the significance level. These findings indicate the absence of differences in the perception of the fission illusion between patients with a right-sided VFD (left-hemispheric lesion) and a left-sided VFD (right-hemispheric lesion).

[Figure 2 about here]

2.6.2. Fusion Illusion

Figure 2B shows that only right-brain-damaged patients with left USN experienced the fusion illusion, with all flash-beep pairings, while healthy controls and VFD patients did not exhibit any fusion effect. The ANOVA showed significant effects of the main factors *Flash* ($F_{2,56}$ = 132.72, *P* < 0.0001, $p\eta^2$ = 0.83), *Beep* ($F_{1,28}$ = 10.25, *P* = 0.004, $p\eta^2$ = 0.28), and *Group* ($F_{2,28}$ = 7.92, *P* < 0.01, $p\eta^2$ = 0.26). The *Group* by *Flash* interaction was significant ($F_{4,56}$ = 7.28, *P* = 0.0001, $p\eta^2$ = 0.42): post-hoc multiple comparisons showed that the higher was the number of flashes presented, the higher was the number of flashes reported by both control participants and VFD patients (from

2 vs. 3 vs. 4 flashes, all *P*s < 0.001); USN patients showed a significant increase of reported flashes only from 2 (1.57) to 4 flashes (2.07, $P < 0.001$); however, no difference between groups was found for any flash condition (all *Ps* > 0.4). Importantly, the *Group* by *Beep* interaction ($F_{2,28} = 7.67$, $P = 0.002$, $p\eta^2 = 0.32$) was also significant: a significant difference between 0 beep and 1 beep trials emerged only in USN patients (B0 = 2.03 *vs.* B1= 1.60, $P = 0.001$), while in controls and VFD patients the sound did not change the number of seen flashes (*Ps* > 0.9 for all comparisons). The *Flash* by *Beep* ($F_{2,56} = 0.42$, $P = 0.65$, $p\eta^2 = 0.02$), and *Flash* by *Beep* by *Group* interactions ($F_{4,56} = 1.65$, $P = 0.17$, $p\eta^2 = 0.04$) did not attain the significance level.

The ANOVA assessing hemispheric asymmetries in the fusion illusion between patients with a left-sided VFD and a right-sided VFD showed a significant effect of the main factor *Flash* ($F_{2,18} = 114.06$, $P = 0.0001$, $p\eta^2 = 0.93$), confirming the relationship between the number of presented and the number of reported flashes. The main factor *Beep* was not significant ($F_{1,9} = 0.03$, $P = 0.88$, $p\eta^2 = 0.01$), further confirming that the sound did not bring about any fusion illusion in VFD patients. Finally, there was no significant effect of the main factor *Half-field* ($F_{1,9} = 0.19$, $P = 0.7$, $p\eta^2 = 0.02$); also the *Half-field* by *Beep* ($F_{1,9} = 0.31$, $P = 0.6$, $p\eta^2 = 0.03$), *Half-field* by *Flash* ($F_{2,18} = 1.17$, $P = 0.2$, $p\eta^2 = 0.16$), and *Half-field by Flash* by *Beep* ($F_{2,18} = 0.11$, $P = 0.9$, $p\eta^2 = 0.01$) interactions were not significant.

2.6.3. Association between lesion profile, time elapsed from stroke and illusory effects

The volume of the occipital, parietal, temporal and frontal lobe lesions (cc^3) in brain-damaged patients with VFD without USN, and in brain-damaged patients with left USN, was measured by calculating the number of damaged voxel in each lobe (Rorden and Brett, 2000; see also, e.g., Bolognini et al., 2012; 2015b); then, a multiple regression was run to predict fission and fusion illusions from the size of the lesion affecting the occipital, parietal, temporal and frontal lobes. To this aim, a *Fission Illusion Index* was computed by subtracting the mean number of seen flashes in 0-beep (F1B0) trials from the mean number of seen flashes in each of the three multiple-

beep trial conditions (F1B2, F1B3, F1B4), and then averaging the differences; positive values indicated a fission effect. The Fusion Illusion Index was calculated by subtracting the mean number of seen flashes in the 0 beep trials from the mean number of seen flashes in the 1 beep trials (i.e., B1 minus B0) in each of the three multiple flashes trial conditions (F2, F3, F4), and then averaging the differences; negative values indicated the presence of the fusion effect.

As shown in Figure 3, the size of the occipital lesion significantly predicted the fission illusion (β coefficient= -0.508, partial r= -0.53, t= -2.33, *P*= 0.035). Conversely, the sizes of the lesions involving the parietal (β= 0.85, partial r= 0.26, t= 1.01, *P*= 0.33), the frontal (β= -0.72, partial r= -0.32, t= -1.27, *P*= 0.23) and the temporal lobes (β= -0.39, partial r= -0.19, t= -0.72, *P*= 0.48) did not predict the fission illusion. For the fusion illusion, no association was found with the lesion site (occipital lobe: β= -0.44, partial r= -0.05, t= -0.18, *P*= 0.86; parietal lobe: β= 0.56, partial r= 0.15, t= 0.59, *P*= 0.57; frontal lobe: β= -0.73, partial r= -0.29, t= -1.15, *P*= 0.27; temporal lobe: β= -0.198, partial r= -0.09, t= -0.32, *P*= 0.75).

Finally, we assessed whether the Fission and Fusion Illusion Indexes were correlated with each other, as well as with the duration of disease in brain-damaged patients (time elapsed from stroke to testing, in months, see Table 1) using Pearson's correlations. Results did not show significant correlations between the fission and the fusion effects in either brain-damaged patients (r= -0.31, *P*= 0.19) or healthy controls (r= 0.22, p= 0.48), further suggesting the independence of the two illusions. Additionally, the duration of disease in brain-damaged patients was not associated either with the Fission (r= -.13, p= .59) or the Fusion (r= .04, p= .88) Illusion Indexes.

[Figure 3 about here]

3. CONTROL EXPERIMENT

3.1. Materials and Method

An additional experiment in healthy adult participants was performed to further assess the influence of age and gender on the fission and fusion illusions. The previous experiment did not show a reliable fusion illusion in healthy participants. It should be considered, however, that the present sample included individuals older than those tested in previous studies assessing the SIFI (e.g., Shams et al., 2000, 2002, 2005; Andersen et al., 2004, 2005; Mishra et al., 2008; Watkins et al., 2006; Bolognini et al., 2011; Kamke et al., 2012; Hamilton et al., 2013). Therefore, the possible impact of age on the ability to perceive the fission and fusion illusions was investigated.

Thirty-five adult healthy participants entered this control study: 15 participants (7 males) were older than 50 years (mean age = 64.53 ± 10.55 years, range = 50-80; mean years of schooling = 7.43 ± 4.5, range = 5-18); 20 participants (9 males) were younger than 30 years (mean age = 23.95 ± 2.31 years, range = 20-30; mean years of schooling = 16.21 ± 2.37, range = 13-19). All participants had normal hearing, no history of hearing disorders, and a normal or corrected-to-normal vision. Materials, methods and statistical analyses were identical to those of the previous experiment.

3.2. Results

For the fission illusion, the participants' mean responses (number of seen flashes) to 1 flash trials were submitted to a 3-way repeated measures ANOVA, with the 5-level *Beep* as the within-subject factor, and the 2-level factors *Age* (≥50 years vs. ≤ 50 years), and *Sex* (male vs. female), as the between-subjects factors. Similarly, for the fusion illusion, the mean number of seen flashes was analyzed with a 4-way ANOVA, with *Beep* and *Flash* as the within-subject factors, and *Age* and *Sex* as the between-subjects factors.

For the fission illusion (Figure 4A), overall all participants' groups exhibited the illusory effect. The ANOVA showed a significant effect of the main factor *Beep* ($F_{4,124} = 52.91$, $P < 0.0001$,

$p\eta^2$ = 0.62). The main effects of *Sex* ($F_{1,31}$= 0.28, *P* = 0.59, $p\eta^2$ = 0.01), and *Age* ($F_{1,31}$= 0.04, *P* = 0.84, $p\eta^2$ = 0.01) were not significant, while the *Age* by *Beep* interaction ($F_{4,124}$ = 6.88, *P* < 0.0001, $p\eta^2$ = 0.28) was significant. Post-hoc comparisons showed that in older participants adding 2, 3, or 4 beeps increased the number of seen flashes, as compared to both 0 beep, and 1 beep conditions (F1B0 = 1.15 and F1B1 = 1.22, *vs.* F1B2 = 1.63, F1B3= 2.13, F1B4 = 2.23, all *Ps* < 0.001). In younger participants, all the illusory trials differed from the 1 beep condition (F1B1 = 1.27 *vs.* F1B2 = 1.76, F1B3= 1.84, F1B4 = 1.88, all *Ps* < 0.01), while only 3 and 4 beeps increased the number of seen flashes (F1B3= 1.84, F1B4 = 1.88, all *Ps* < 0.01) as compared to the 0 beep condition (F1B0= 1.47 vs. F1B3= 1.84, F1B4 = 1.88, all *Ps* < 0.01). However, there was no difference between groups in the number of seen flashes in both the illusory and the non-illusory trials (older vs. younger in each non-illusory and illusory trial, all *Ps* > 0.6). All other interactions did not attain the significance level: *Sex* by *Age* ($F_{1,31}$= 0.43, *P* = 0.52, $p\eta^2$ = 0.01), *Sex* by *Beep* ($F_{4,124}$= 1.61, *P* = 0.17, $p\eta^2$ = 0.05), *Sex* by *Age* by Beep ($F_{4,124}$= 0.65, *P* = 0.63, $p\eta^2$ = 0.02).

As for the fusion illusion (Figure 4B), young, but not old, participants, showed the illusory effect. The ANOVA showed significant effects of the main factors *Flash* ($F_{2,62}$ = 164.03, *P* < 0.0001, $p\eta^2$ = 0.84), *Beep* ($F_{1,31}$ = 9.38, *P* < 0.01, $p\eta^2$ = 0.23), and *Age* ($F_{1,31}$ = 12.27, *P* < 0.01, $p\eta^2$ = 0.29), as well as of the *Age* by *Beep* interaction ($F_{1,31}$ = 9.50, *P* < 0.004, $p\eta^2$ = 0.25). Post-hoc comparisons showed the absence of the fusion illusion in older participants (B0 = 2.24 *vs.* B1 = 2.23, *P* = 0.9); conversely, the presence of the beep yielded a reliable fusion effect in younger participants (B0 = 2.89 *vs.* B1 = 2.69, *P* < 0.001). The effect of the main factor *Sex* ($F_{1,31}$ = 0.66, *P* = 0.42, $p\eta^2$ = 0.02) was not significant. The interactions *Sex* by *Age* ($F_{1,31}$ = 1.51, *P* = 0.22, $p\eta^2$ = 0.05), *Sex* by *Flash* ($F_{2,62}$ = 0.60, *P* = 0.55, $p\eta^2$ = 0.02), *Age* by *Flash* ($F_{2,62}$ = 0.05, *P* = 0.94, $p\eta^2$ = 0.01), *Sex* by *Beep* ($F_{1,31}$= 0.45, *P* = 0.50, $p\eta^2$ = 0.01), *Beep* by *Flash* ($F_{2,62}$ = 0.48, *P* = 0.62, $p\eta^2$ = 0.02), *Sex* by *Age* by *Flash* ($F_{2,62}$ = 0.56, *P* = 0.58, $p\eta^2$ = 0.02), *Sex* by *Age* by *Beep* ($F_{1,31}$= 0.02, *P* = 0.89, $p\eta^2$ = 0.01), *Sex* by *Beep* by *Flash* ($F_{2,62}$ = 2.22, *P* = 0.11, $p\eta^2$ = 0.07), *Age* by *Beep* by *Flash*

($F_{2,62}$ = 1.23, *P* = 0.29, $p\eta^2$ = 0.04), and *Sex* by *Age* by *Beep* by *Flash* ($F_{2,62}$ = 0.17, *P* = 0.84, $p\eta^2$ = 0.01) were also not significant.

The fission and fusion illusory effects, as computed by the respective Illusion Indexes, were not correlated both in old (r= -0.39, *P*= 0.15), and in young (r= -0.38, *P*= 0.09) participants.

Summarizing, the control experiment in healthy participants confirmed that the fusion illusion is lost in the elderly, while the fission illusion emerges in both groups in a similar fashion. Males and females do not differently perceive fission and fusion illusions.

[Figure 4 about here]

4. Discussion

In this study we show that the crossmodal illusory alterations of visual perception, brought about by auditory stimuli in the SIFI, differ in a number of important aspects in brain-damaged patients with homonymous contralesional VFD (without USN), and in right-brain-damaged patients with left USN. First, as compared to controls, the fission illusion is reduced in left- and right-brain-damaged patients with VFD, with no hemispheric asymmetries, but preserved in right-brain-damaged patients with left USN. Specifically, the illusory perception of multiple flashes requires more than two beeps to emerge in brain-damaged patients with VFD, but not in the other groups. Even when three or four beeps are presented, fission effects are still reduced in brain-damaged patients with VFD, as compared to healthy participants and right-brain-damaged patients with USN. On the other hand, a reliable and powerful fusion illusion is evoked in USN patients only, but neither in patients with VFD, nor in healthy controls. This pattern of results indicates that fission and fusion effects are dissociable crossmodal phenomena, differently modulated by impairments of visual perception, as in brain-damaged patients with VFD without USN, and in right-brain-damaged patients with a higher-order deficit of spatial attention (left USN), and, in turn, by the different lesion profiles featuring these disorders.

The reduction of the fission illusion observed in patients with VFD suggests that the integrity of the primary visual areas is important for the illusory perceptual experience of the fission of the visual stimulus by multiple sounds. Indeed, the amount of the lesion affecting the occipital cortex predicts the patients' perception of the fission illusion: in other words, the larger is the occipital damage, the weaker is the fission illusion. Importantly, the fission illusion is reduced in VFD patients regardless of the laterality of the hemispheric lesion. The lack of hemispheric asymmetries points to a lower-level (sensory) functional locus of the fission illusion. In line with this conclusion, the fission illusion is fully preserved in right-hemisphere-damaged patients with left USN, who suffer from higher-level spatial and attentional deficits (Vallar and Bolognini, 2014).

Overall, these findings indicate that an occipital lesion can disrupt audio-visual interactions in the temporal domain, which are at the basis of the fission illusion. Visual cortical areas represent a core substrate for the binding of visual and auditory signals for the fission illusion. However, occipital areas work in concert with heteromodal association areas, such as the STS and the PPC to give rise to the fission illusion (Shams et al., 2001; Watkins et al., 2006; Mishra et al., 2007; 2010). The STS and PPC areas were not systematically damaged in our sample of VFD patients, possibly explaining why we observed a residual fission illusion in VFD participants.

Critically, the reduction of the fission illusion in brain-damaged patients with VFD cannot be attributed to primary sensory impairments, such as impaired stimulus detection. Indeed, the number of reported flashes in the unimodal non-illusory single and multiple flash trials (with no beep being presented) is comparable in healthy participants and VFD patients: the groups differ only in the processing of crossmodal illusory stimuli (see Figure 2). This conclusion is further supported by the finding that the only right-brain-damaged patient with left USN also showing a left VFD (P14) exhibited illusory effects, comparable to those of the other right-brain-damaged patients with left USN. It is remarkable that, in the same patient, the lesion spared the occipital lobe, hence his visual field impairment is more compatible with a pseudo-hemianopia related to the severe USN

(Vallar and Bolognini, 2014), rather than advocating the presence of a pure primary sensory deficits.

Conversely, right-brain-damaged patients with left USN show a disproportionately amplified and reliable fusion illusion, relative to healthy controls and VFD patients. Therefore, audio-visual integration of temporal information, as indexed by the fusion illusion, appears to be preserved in right-brain-damaged patients with left USN. Unimodal temporal processing of visual stimuli has been, however, reported to be impaired in the USN syndrome (e.g., Harrington et al., 1998; Magnani et al., 2011; Danckert et al., 2007). It is also of interest that a number of illusions are largely spared in USN patients, including the ventriloquism illusion (Bertelson et al., 2000), the visual Müller-Lyer illusion (Vallar et al. 2000; Daini et al., 2002), a visuo-tactile variant of it (Mancini et al., 2011), the Mirror Box Illusion (Dohle et al., 2009), and the Rubber Hand Illusion (Kitadono and Humphreys, 2007; Bolognini et al. 2014, 2015a). One possible explanation is that the hyper-susceptibility to crossmodal illusions by patients with left USN may be related to the pathological over-excitability of parietal-frontal functional connections in intact left-hemispheric regions, which was found in right-brain-damaged patients with left USN (Koch et al. 2008, 2013).

The fission and the fusion illusions may *prima facie* appear as complementary phenomena. The present neuropsychological findings from brain-damaged patients converge with behavioral, neuroimaging, and electrophysiological evidence, indicating that different neural mechanisms underlie these illusions (Andersen et al., 2004; Innes-Brown and Crewther, 2009; Shams et al., 2000; Mishra et al., 2008; Watkins et al., 2007).

At the behavioral level, in healthy participants, the fusion illusion seems overall less reliable and weaker than the fission illusion, and also more vulnerable to inter-individual variability (Shams et al., 2000; Andersen et al., 2004, 2005; Mishra et al., 2008; Innes-Brown and Crewther, 2009); we also did not find evidence for a correlation between the two illusions in both healthy (old and young) individuals and in brain-damaged patients. Moreover, aging seems to differently influence the perception of ‘fission’ and ‘fusion’ illusions: a larger susceptibility to fission effects, as

compared with fusion effects, was recently described in older participant (over 65 years, and of an average age comparable to that of our healthy participants), as compared with younger (18-30 years) adults (McGovern et al., 2014; DeLoss and Andersen 2015). Our control experiment in healthy participants confirms that the fission illusion is overall similar in younger (< 30 years) and older adults (> 50 years), while the fusion illusion seems to be lost in the elderly. These findings are in line with recent evidence pointing to dissociable age-related effects in multisensory processing (review in Mozolic et al., 2012), and they also strengthen the reliability of our findings in right-brain-damaged patients with left USN, supporting the view that the greater susceptibility of these patients to the fusion illusion cannot be merely attributed to age differences (note that our USN patients were, on average, even older than VFD patients and than healthy controls).

At the neural level, different brain areas and mechanisms are recruited by the two illusory phenomena. The fission illusion is primarily related to early, short-latency auditory modulation of the activity of the primary visual areas, occurring around 30-60 msec after stimulus onset (Arden et al, 2003; Shams et al., 2005; Mishra et al., 2007; Cuppini et al., 2014). These early cross-modal interactions are likely to be supported by anatomical feed-forward projections connecting the primary auditory and visual areas (Cappe and Barone, 2005; Falchier et al., 2002; Rockland and Ojima, 2003; Clavagnier et al., 2004; see also Bolognini et al., 2013b for TMS evidence), which are influenced by modulatory feedback projections from multisensory regions in the temporal and parietal cortices (Shams et al., 2001; Watkins et al., 2006; Mishra et al., 2007; 2010). This evidence is largely consistent with the negative correlation between the fission illusion and the size of the occipital damage. Conversely, the fusion illusion is characterized by a different spatio-temporal profile, namely a later crossmodal modulation of the activity of the STG (around 80–112 msec), and of the extrastriate visual cortex (i.e., 228–248 msec after stimulus onset) (Mishra et al., 2008).

Interestingly, even the ventriloquist's illusion is absent in brain-damaged patients with VFD without USN (Leo et al., 2008), but preserved in right-brain-damaged patients with left USN (Bertelson et al., 2000). Together with the present findings, these observations suggest that the

visual cortex is a neural underpinning of crossmodal audio-visual illusions concerning temporal (SIFI) and spatial (ventriloquist) perception. After an occipital damage resulting in VFD, visual processing cannot be influenced effectively by auditory stimuli in temporal perception, as in the SIFI, but it is unable to modulate auditory processing in spatial perception, as indexed by the ventriloquist's illusion. Instead, multisensory integrative functions are still active after brain damage affecting a right-hemisphere-based fronto-parietal network (comprising the premotor, posterior-inferior parietal and superior posterior temporal cortices) for spatial attention and awareness of sensory inputs. Damage to these neural systems is a main neural underpinning of the USN syndrome (Corbetta and Shulman, 2011; Vallar and Bolognini, 2014).

To conclude, the integrity of occipital cortical activity is a crucial factor for the fission illusion to occur, while the same illusion is not precluded by the dysfunction of a higher-order supramodal network responsible for spatial attention and awareness. Conversely, the fusion illusion appears even facilitated by a dysfunctional activity of higher-order multisensory fronto-temporo-parietal regions, which does not perturb the integration of audio-visual inputs in the temporal domain.

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References

Andersen, T.S., Tiippana, K., Sams, M., 2004. Factors influencing audiovisual fission and fusion illusions. *Cogn. Brain Res.* 21 (3), 301-308.

Andersen, T.S., Tiippana, K., Sams, M., 2005. Maximum likelihood integration of rapid flashes and beeps. *Neurosci. Lett*. 380 (1-2), 155-160.

Arden, G.B., Wolf, J.E., Messiter, C., 2003. Electrical activity in visual cortex associated with combined auditory and visual stimulation in temporal sequences known to be associated with a visual illusion. *Vision Res.* 43 (23), 2469-2478.

Bertelson, P., Pavani, F., Ladavas, E., Vroomen, J., de Gelder, B., 2000. Ventriloquism in patients with unilateral visual neglect. *Neuropsychologia* 38 (12), 1634-1642.

Bisiach, E., Faglioni, P., 1974. Recognition of random shapes by patients with unilateral lesions as a function of complexity, association value and delay. *Cortex* 10 (2), 101-110.

Bisiach, E., Cappa, S. F., and Vallar, G. (1983). *Guida all'esame neuropsicologico.* Raffaello Cortina, Milano.

Bisiach, E., Cornacchia, L., Sterzi, R., Vallar, G., 1984. Disorders of perceived auditory lateralization after lesions of the right hemisphere. *Brain* 107 (Pt 1), 37–52.

Bolognini, N., Rasi, F., Coccia, M., Ladavas, E., 2005. Visual search improvement in hemianopic patients after audio-visual stimulation. *Brain* 128 (Pt 12), 2830-2842.

Bolognini, N., Rossetti, A., Casati, C., Mancini, F., Vallar, G., 2011. Neuromodulation of multisensory perception: a tDCS study of the sound-induced flash illusion. *Neuropsychologia* 49 (2), 231-237.

Bolognini N., Casanova D., Maravita A., Vallar G., 2012. Bisecting real and fake body parts: effects of prism adaptation after right brain damage. *Front. Hum. Neurosci.* 6, 154.

Bolognini, N., Convento, S., Rossetti, A., Merabet, L.B., 2013a. Multisensory processing after a brain damage: clues on post-injury crossmodal plasticity from neuropsychology. *Neurosci. Biobeh. Rev.* 37 (3), 269□278.

Bolognini, N., Convento, S., Fusaro, M., Vallar, G., 2013b. The sound-induced phosphene illusion. *Exp. Brain Res.*, 231 (4), 469-478.

Bolognini, N., Ronchi, R., Casati, C., Fortis, P., Vallar, G., 2014. Multisensory remission of somatoparaphrenic delusion: My hand is back! *Neurology: Clinical Practice*, 4(3), 216–225.

Bolognini N., Russo C., Vallar G., 2015 a. Crossmodal Illusions in Neurorehabilitation. *Front. Behav. Neurosci.* 9, 212.

Bolognini, N., Convento, S., Banco, E., Mattioli, F., Tesio, L., Vallar, G., 2015 b. Improving ideomotor limb apraxia by electrical stimulation of the left posterior parietal cortex. *Brain,* 138 (Pt 2), 428-439.

Brighina, F., Bolognini, N., Cosentino, G., Maccora ,S., Paladino, P., Baschi, R., Vallar, G., Fierro B., 2015. Visual cortex hyperexcitability in migraine in response to sound-induced flash illusions. *Neurology*, 84 (20), 2057-2061.

Brozzoli, C., Dematte, M.L., Pavani, F., Frassinetti, F., Farne, A., 2006. Neglect and extinction: within and between sensory modalities. *Restor. Neurol. Neurosci.* 24 (4-6), 217-232.

Cappe, C., Barone, P., 2005. Heteromodal connections supporting multisensory integration at low levels of cortical processing in the monkey. *Eur. J. Neurosci.* 22 (11), 2886□2902.

Clavagnier, S., Falchier, A., Kennedy, H., 2004. Long-distance feedback projections to area V1: Implications for multisensory integration, spatial awareness, and visual consciousness. *Cogn. Affect. Behav. Neurosci.* 4 (2), 117-126.

Corbetta, M., Shulman, G.L., 2011. Spatial neglect and attention networks. *Ann. Rev. Neurosci.* 34, 569-599.

Cuppini, C., Magosso, E., Bolognini, N., Vallar, G., & Ursino, M. (2014). A neurocomputational analysis of the sound-induced flash illusion. Neuroimage 92, 248-266.

Daini, R., Angelelli, P., Antonucci, G., Cappa, S.F., Vallar, G., 2002. Exploring the syndrome of spatial unilateral neglect through an illusion of length. *Exp. Brain Res.* 144 (2), 224-237.

Danckert, J., Ferber, S., Pun, C., Broderick, C., Striemer, C., Rock, S., Stewart, D., 2007. Neglected time: impaired temporal perception of multisecond intervals in unilateral neglect. *J. Cogn. Neurosci.* 19 (10), 1706-1720.

De Renzi, E., 1982. *Disorders of space exploration and cognition*. John Wiley, Chichester.

DeLoss, DJ., Andersen, G.J. (2015). Aging, Spatial Disparity, and the Sound-Induced Flash Illusion. PLoS One 10 (11):e0143773.

Diller, L., Weinberg, J., 1977. Hemi-inattention in rehabilitation. The evolution of a rational remediation program. In E.A. Weinstein R.P. Friedland (Eds.), Hemi-inattention and hemisphere specialization. New York, NY: Raven Press.

Dohle, C., Püllen, J., Nakaten, A., Küst, J., Rietz, C., Karbe, H., 2009. Mirror therapy promotes recovery from severe hemiparesis: a randomized controlled trial. *Neurorehab. and Neural Rep.* 23 (3), 209-217.

Falchier, A., Clavagnier, S., Barone, P., Kennedy, H., 2002. Anatomical evidence of multimodal integration in primate striate cortex. *J. Neurosci.* 22 (13), 5749□5759.

Fortis, P., Maravita, A., Gallucci, M., Ronchi, R., Grassi, E., Senna, I., Olgiati, E., Perucca, L., Banco, E., Posteraro, L., Tesio, L., Vallar, G. 2010. Rehabilitating patients with left spatial neglect by prism exposure during a visuomotor activity. *Neuropsychology* 24 (6), 681-697.

Fraser, J. A., Newman, N. J., Biousse, V., 2011. Disorders of the optic tract, radiation, and occipital lobe. *Handb. Clin. Neurol.*102, 205–21.

Frassinetti, F., Bolognini, N., Bottari, D., Bonora, A., Làdavas, E., 2005. Audiovisual integration in patients with visual deficit. *J. Cogn. Neurosci.* 17 (9), 1442-1452.

Gainotti, G., Messerli, P., Tissot, R., 1972. Qualitative analysis of unilateral spatial neglect in relation to laterality of cerebral lesions. *J. Neurol. Neurosurg. Psychiatry* 35 (4), 545-550.

Gainotti, G., 2010. The role of automatic orienting of attention towards ipsilesional stimuli in non-visual (tactile and auditory) neglect: a critical review. *Cortex*, 46(2), 150–160.

Gauthier, L., Dehaut, F., Joanette, Y., 1989. The Bells Test: A quantitative and qualitative test for visual neglect. *Int. J. Clin. Neuropsych.* 11, 49-54.

Hamilton, R.H., Wiener, M., Drebing, D.E., Coslett, H.B., 2013. Gone in a flash: manipulation of audiovisual temporal integration using transcranial magnetic stimulation. *Front. Psychol.* 4, 571.

Harrington, D.L., Haaland, K.Y., Knight, R.T., 1998. Cortical networks underlying mechanisms of time perception. *J. Neurosci.* 18 (3), 1085-1095.

Howard, I.P., Templeton, W.B., 1966. Human Spatial Orientation. Wiley, London.

Innes-Brown, H., Crewther, D., 2009. The Impact of Spatial Incongruence on an Auditory-Visual Illusion. *PLoS One* 4 (7), e6450.

Jacobs, S., Brozzoli, C., Farnè, A., 2012. Neglect: a multisensory deficit? *Neuropsychologia* 50 (6), 1029-44.

Leo, F., Bolognini, N., Passamonti, C., Stein, B.E., Ladavas, E., 2008. Cross-modal localization in hemianopia: new insights on multisensory integration. *Brain* 131 (Pt 3), 855-865.

Lewald, J., Peters, S., Tegenthoff, M., Hausmann, M., 2009 a. Dissociation of auditory and visual straight ahead in hemianopia. *Brain Res.*1287, 111-117.

Lewald, J., Peters, S., Tegenthoff, M., Hausmann, M., 2009 b. Distortion of auditory space in hemianopia. *Eur. J. Neurosci.* 30 (7), 1401-1411.

Kamke, M.R., Vieth, H.E., Cottrell, D., Mattingley, J.B., 2012. Parietal disruption alters audiovisual binding in the sound-induced flash illusion. *Neuroimage* 62 (3), 1334-1341.

Keller, L., Lefin-Rank, G., 2010. Improvement of visual search after audiovisual exploration training in hemianopic patients. *Neurorehab. Neural Rep.* 24 /7), 666-673.

Kitadono, K., Humphreys, G.W., 2007. Short-term effects of the 'rubber hand' illusion on aspects of visual neglect. *Neurocase* 13 (4), 260-271.

Koch, G., Oliveri, M., Cheeran, B., Ruge, D., Lo Gerfo, E., Salerno, S., Torriero, S., Marconi, B., Mori, F., Driver, J., Rothwell, J.C., Caltagirone, C., 2008. Hyperexcitability of parietal-motor

functional connections in the intact left-hemisphere of patients with neglect. *Brain*, 131(Pt 12), 3147-3155.

Koch, G., Veniero, D., Caltagirone, C., 2013. To the other side of the neglected brain: the hyperexcitability of the left intact hemisphere. *Neuroscientist*, 19 (2), 208-217.

Mancini, F., Bricolo, E., Mattioli, F.C., Vallar, G., 2011. Visuo-haptic interactions in unilateral spatial neglect: the cross modal judd illusion. *Front. Psychol.* 2, 341.

Magnani, B., Oliveri, M., Mancuso, G., Galante, E., Frassinetti, F., 2011. Time and spatial attention: effects of prism adaptation on temporal deficits in brain damaged patients. *Neuropsychologia* 49 (5), 1016-1023.

McGovern, D.P., Roudaia, E., Stapleton, J., McGinnity, T.M., Newell, F.N. (2014). The sound-induced flash illusion reveals dissociable age-related effects in multisensory integration. *Front. Aging Neurosci.* 6, 250.

Mishra, J., Martinez, A., Hillyard, S.A., 2008. Cortical processes underlying sound induced flash fusion. *Brain Res.* 1242, 102-115.

Mishra, J., Martinez, A., Sejnowski, T.J., Hillyard, S.A., 2007. Early cross-modal interactions in auditory and visual cortex underlie a sound-induced visual illusion. *J. Neurosci.* 27 (15), 4120-4131.

Mishra, J., Martinez, A., Hillyard, S.A., 2010. Effect of attention on early cortical processes associated with the sound-induced extra flash illusion. *J. Cogn. Neurosci.* 8, 1714-1729.

Mozolic, J.L., Hugenschmidt, C.E., Peiffer, A.M., Laurienti, P.J., 2012. Multisensory Integration and Aging. In: M. M. Murray MM, M.T. Wallace (Eds.). *The Neural Bases of Multisensory Processes* (Chapter 20). Boca Raton (FL): CRC Press/Taylor & Francis.

Passamonti, C., Bertini, C., Làdavas, E., 2009. Audio-visual stimulation improves oculomotor patterns in patients with hemianopia. *Neuropsychologia* 47 (2), 546-555.

Pavani, F., Ladavas, E., Driver, J., 2003. Auditory and multisensory aspects of visuospatial neglect. *Trends Cogn. Sci.*, 7 (9), 407-414.

Rockland, K.S., Ojima, H., 2003. Multisensory convergence in calcarine visual areas in macaque monkey. *Int. J. Psychophysiol.* 50 (1-2), 19-26.

Rode, G., Michel, C., Rossetti, Y., Boisson, D., Vallar, G., 2006. Left size distortion (hyperschematia) after right brain damage. *Neurology* 67 (10), 1801-1808.

Rorden, C., Brett, M., 2000. Stereotaxic display of brain lesions. *Behav. Neurol.* 12 (4), 191-200.

Schendel, K., Robertson, L.C., 2004. Reaching out to see: arm position can attenuate human visual loss. *J. Cogn. Neurosci.* 16 (6), 935-43.

Shams, L., Kamitani, Y., Shimojo, S., 2000. What you see is what you hear. *Nature* 408 (6814), 788.

Shams, L., Kamitani, Y., Thompson, S., Shimojo, S., 2001. Sound alters visual evoked potentials in humans. *Neuroreport* 12 (17), 3849-3852.

Shams, L., Kamitani, Y., Shimojo, S., 2002. Visual illusion induced by sound. *Cogn. Brain Res.* 14 (1), 147-152.

Shams, L., Iwaki, S., Chawla, A., Bhattacharya, J., 2005. Early modulation of visual cortex by sound: an MEG study. *Neurosci. Lett.* 378, 76-81.

Shams, L., Kim, R., 2011. Crossmodal influences on visual perception. *Phys. Life Rev.* 7 (3), 269-284.

Tinelli, F., Purpura, G., Cioni, G., 2015. Audio-Visual Stimulation Improves Visual Search Abilities in Hemianopia due to Childhood Acquired Brain Lesions. *Multisensory Res.* 28 (1-2), 153-71.

Thurlow, W.R., Jack, C.E., 1973. Certain determinants of the "ventriloquism effect". *Percept Mot. Skills*, 36 (3), 1171-1184.

Vallar, G., Rusconi, M.L., Fontana, S., Musicco, M., 1994. Three clinical tests for the assessment of visuo-spatial exploration. Norms from 212 normal subjects. *Archivio di Psicologia, Neurologia e Psichiatria* 55 (5), 827-841.

Vallar, G., Daini, R., Antonucci, G., 2000. Processing of illusion of length in spatial hemineglect. A study of line bisection. *Neuropsychologia* 38 (7), 1087–1097.

Vallar G., Bolognini N., 2014. Unilateral spatial neglect. In: A.C. Nobre S. Kastner (Eds.), Oxford Handbook of Attention. Oxford University Press, Oxford.

Warren, D.H., Welch, R.B., McCarthy, T.J., 1981. The role of visual–auditory "compellingness" in the ventriloquism effect: implications for transitivity among the spatial senses. *Percept. Psychophys.* 30 (6), 557-64.

Welch, R.B., Warren, D.H., 1980. Immediate perceptual response to intersensory discrepancy. *Psychol. Bull.*88 (3), 638-667.

Wilson, B., Cockburn, J., Halligan, P.W., 1987. Behavioural Inattention Test. Thames Valley Test, Titchfield, UK.

Watkins, S., Shams, L., Josephs, O., Rees, G., 2007. Activity in human V1 follows multisensory perception. *Neuroimage* 37 (2), 572-578.

Watkins, S., Shams, L., Tanaka, S., Haynes, J.D., Rees, G., 2006. Sound alters activity in human V1 in association with illusory visual perception. *Neuroimage* 31 (3), 1247-1256.

Zihl, J., Kennard, C., 1996. Disorders of higher visual functions. In: Brandt, T., Caplan, L.R., Dichgans, J., Diener, H.C., Kennard, C. (Eds.), Neurological Disorders: Course and Treatment. Academic Press, San Diego.

Zhang, X., Kedar, S., Lynn, M.J., Newman, N.J., Biousse,V, 2006. Natural history of homonymous hemianopia. *Neurology*, 66 (6), 901-905.

Captions to Figures

Figure 1. Overlay lesion plots for (A) stroke patients with VFD without USN (N= 11) and for (B) stroke patients with left USN (N= 7). Each color represents 20% increments, from green areas indicating maximum overlap, pink areas minimum overlap.

Figure 2. (A) Fission and (B) Fusion Illusions in the main experiment: average number of seen flashes (ordinate) in each stimulus condition (abscissa: F = Flash, B= Beep) by healthy controls (dotted black line, N= 12), USN patients (dark grey line, N= 8), and VFD patients (light grey line, N= 11). Error bars= standard error (SE).

Figure 3. Correlation scatterplots for the Fission (A) and Fusion (B) illusions, between the Illusion Index (ordinate; Fission Illusion Index = multiple beeps trials minus 0-beep trials; Fusion Illusion Index = 1-beep trials minus 0-beep trials), and the size of the lesion (abscissa) affecting the occipital, parietal, temporal and frontal lobes (number of damaged voxels in each lobe). Multiple regression analyses showed that the fission illusion was associated to the size of the occipital lesion (*P*= 0.035, see panel A).

Figure 4. (A) Fission and (B) Fusion Illusions in the control experiment: Average number of seen flashes (ordinate) in each stimulus condition (abscissa: F = Flash, B= Beep) in healthy individuals younger than 30 years (grey line, N= 20) and older than 50 years (black line, N= 15). Error bars= SE.

Table 1. Demographic and neurological data and baseline neuropsychological assessment. M/F= male/female. R-/L-VFD= right-/left-sided visual field deficit. USN= Unilateral Spatial Neglect. H/I= haemorrhagic/ischemic stroke; N= neoplastic lesion. Standardised neurological exam: MM/SS/V= motor/somatosensory/visual deficit; E= extinction to double simultaneous stimulation; * = defective score according to available normative data; ° = deficit featured by neglect signs (i.e., contralesional omissions in cancellation and drawing tasks, ipsilesional deviation in the bisection task).

Group	Patient	Age / Sex	Duration of disease (months)	Etiology	Sensori-motor deficits			Line Bisection	Cancellation			Drawing
					MM	V	SS		Bells	Letters	Stars	Complex Figure
R-VFD	P1	69, M	12	H	-	+	-	+2.4%	35/35	104/104	56/56	10/10
	P2	25, F	33	H	-	+	-	+6.8%	35/35	104/104	56/56	10/10
	P3	49, M	10.5	H	-	+	-	+8.6%*°	29/35*	104/104	56/56	10/10
	P4	45, F	12	I	-	+	-	-4%	27/35*	104/104	55/56	10/10
	P5	66, M	14	I	-	+	+	+10.21%*°	35/35	104/104	56/56	9.5/10*
	P6	45,M	9	I	-	+	-	+8.68%*°	35/35	104/104	55/56	9.5/10*
	P7	67, M	11	I	-	+	+	-3.13%	35/35	104/104	56/56	10/10
L-VFD	P8	46, M	3	I	-	+	-	-4.2%*°	35/35	104/104	56/56	10/10
	P9	34, M	6	I	-	+	-	-10.20%	35/35	104/104	56/56	10/10
	P10	45, F	14	I	-	+	-	-18.8%*°	35/35	104/104	56/56	10/10
	P11	65, M	37	I	-	+	-	-0.6%	33/35	102/104	54/56	10/10
USN	P12	51, F	1	H	+	E	+	+6.2%	34/35	46/104*°	45/56*°	9/10*°
	P13	69, M	2	H	-	-	-	+0.4%	24/35*°	102/104	56/56	10/10
	P14	72, M	1	N	+	+	+	+77.4%*°	0/35*°	4/104*°	7/56*°	3/10*°
	P15	83, F	1.5	I	+	-	-	+6.6%	30/35*°	95/104*°	48/56*°	9/10
	P16	76, M	1.5	H	-	-	-	+6.2%	19/35*°	104/104	55/56	8.5/10*°
	P17	73, M	2	I	+	-	-	+29.6%*°	3/35*°	12/104*°	6/56*°	0.5/10*°
	P18	76, M	2	I	+	E	-	+22.2%*°	13/35*°	28/104*°	20/56*°	10/10
	P19	70, M	23	I	+	-	-	+3.8%*°	22/35*°	66/104*°	39/56*°	9.5/10*°

Figure 1

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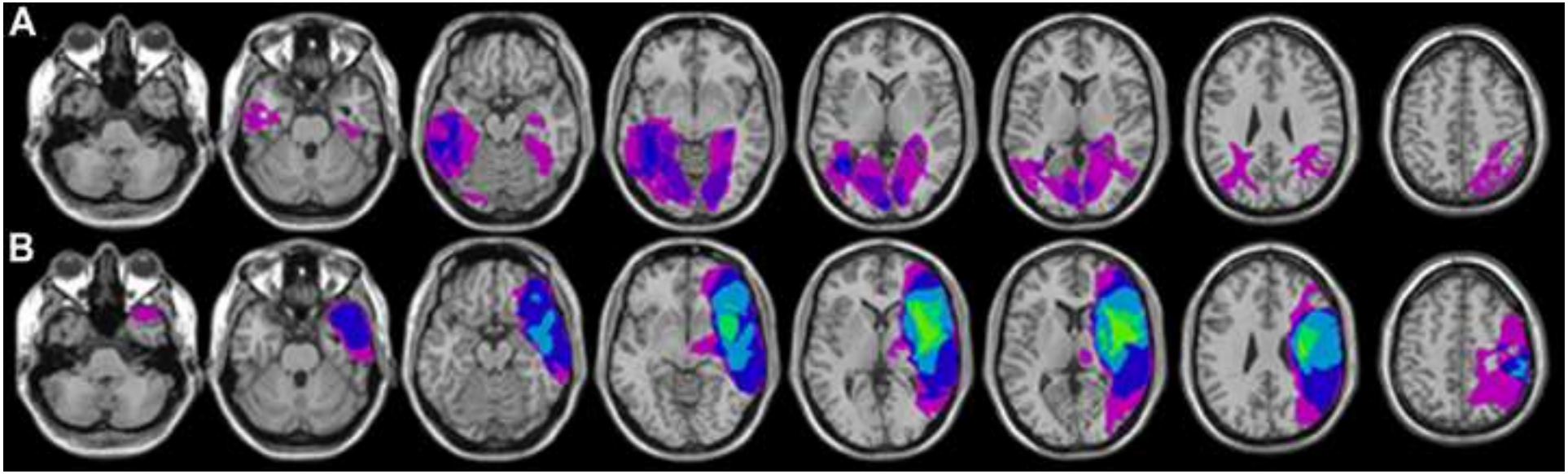

Figure 2

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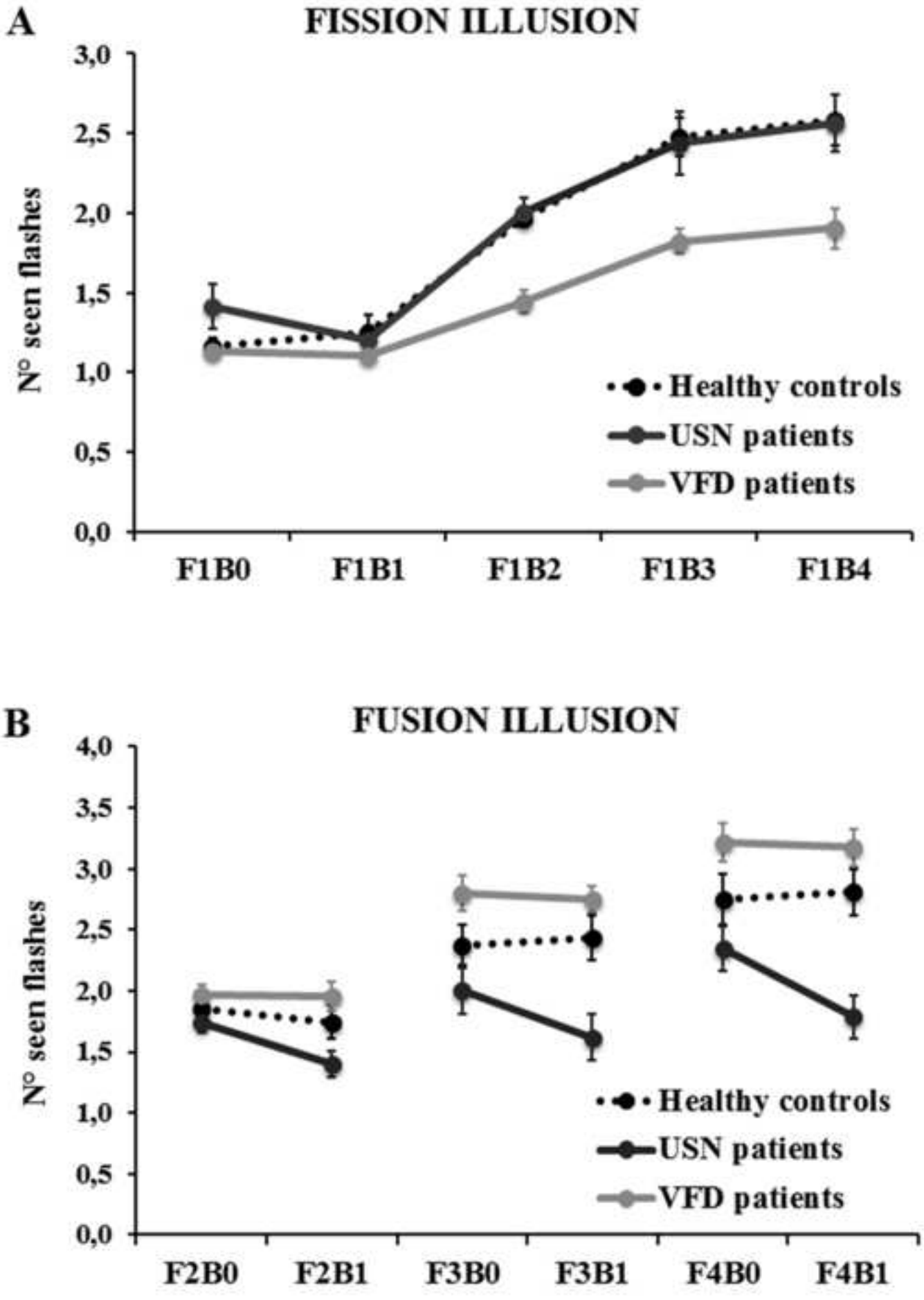

Figure 3

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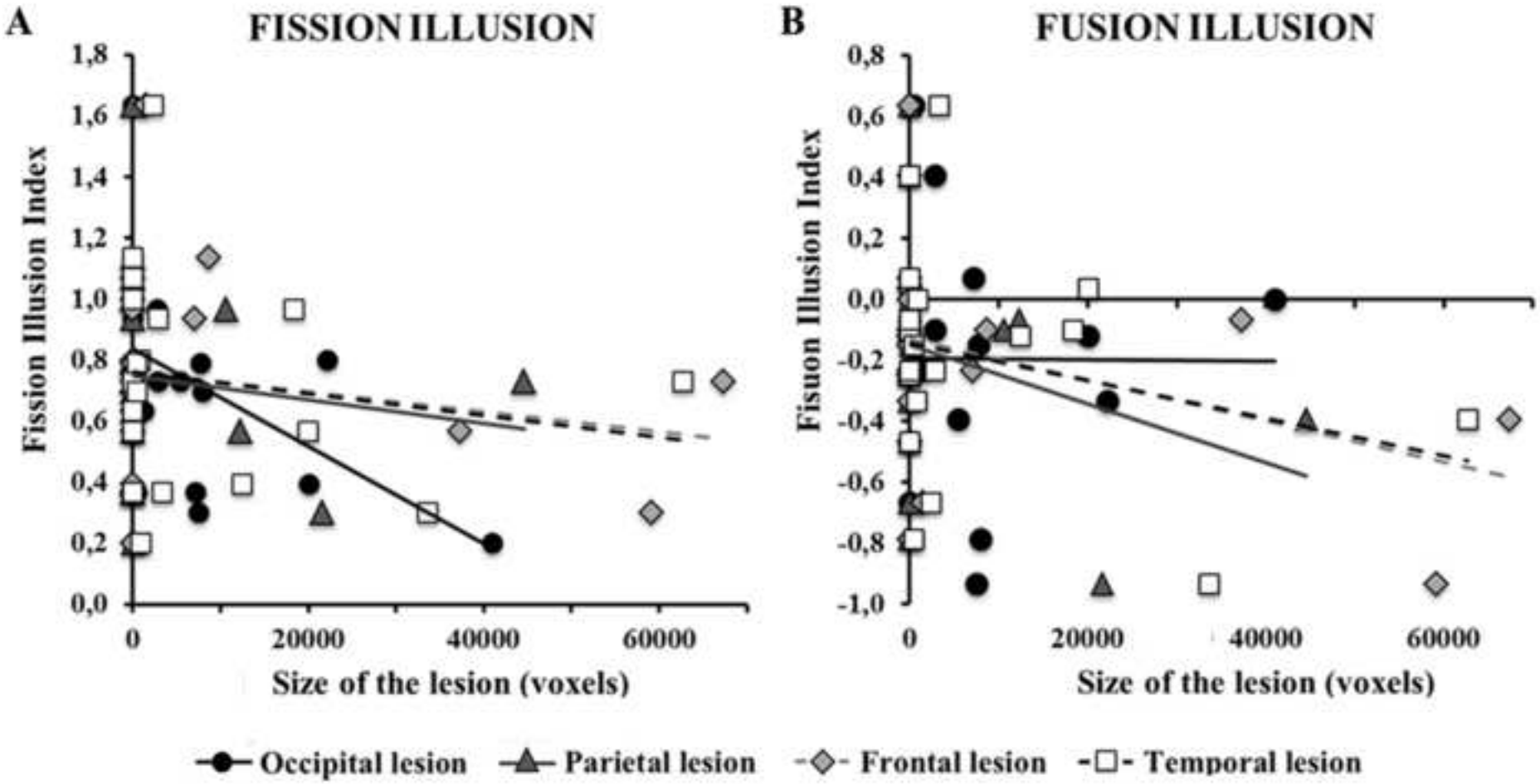

Figure 4

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