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Subliminal galvanic-vestibular stimulation influences ego- and object-centred components of visual neglect

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ABSTRACT

Neglect patients show contralesional deficits in egocentric and object-centred visuospatial tasks. The extent to which these different phenomena are modulated by sensory stimulation remains to be clarified. Subliminal galvanic vestibular stimulation (GVS) induces imperceptible, polarity-specific changes in the cortical vestibular systems without the unpleasant side effects (nystagmus, vertigo) induced by caloric vestibular stimulation. While previous studies showed vestibular stimulation effects on egocentric spatial neglect phenomena, such effects were rarely demonstrated in object-centred neglect. Here, we applied bipolar subsensory GVS over the mastoids (mean intensity: 0.7 mA) to investigate its influence on egocentric (digit cancellation, text copying), object-centred (copy of symmetrical figures), or both (line bisection) components of visual neglect in 24 patients with unilateral right hemisphere stroke. Patients were assigned to two patient groups (impaired vs. normal in the respective task) on the basis of cut-off scores derived from the literature or from normal controls. Both groups performed all tasks under three experimental conditions carried out on three separate days: (a) sham/baseline GVS where no electric current was applied, (b) left cathodal/right anodal (CL/AR) GVS and (c) left anodal/right cathodal (AL/CR) GVS, for a period of 20 min per session. CL/AR GVS significantly improved line bisection and text copying whereas AL/CR GVS significantly ameliorated figure copying and digit cancellation. These GVS effects were selectively observed in the impaired- but not in the unimpaired patient group. In conclusion, subliminal GVS modulates ego- and object-centred components of visual neglect rapidly. Implications for neurorehabilitation are discussed.

1. Introduction

Neglect is a multicomponent syndrome where patients typically fail to explore sensory stimuli in the contralesional hemispace or body side. Neglect most often follows after right-hemispheric lesions (Kerkhoff, 2001) and entails several different components (Grimsen et al., 2008). For example, neglect patients may show severe impairments in a wide range of egocentric tests of neglect including cancellation, visual and tactile exploration as well as writing. These egocentric neglect phenomena can be defined as a failure to attend to contralateral stimuli in space in relation to the body's midsaggital plane. Hence, the body serves as the egocentric anchor or reference (Ventre and Flandrin, 1984) for the patient's performance in space. Another component of neglect is termed object-centred neglect. Here, the contralateral side of a single perceptual object is neglected irrespective of its location relative to the viewer. In contrast to egocentric neglect phenomena, the midline of the object and not the patient's body serves as a reference for tasks like copying a flower or a clock face (Halligan et al., 2003). Finally, some tests may require a combination of both reference frames. In those tests, the contralateral side of a single perceptual object is neglected but the spatial location of the stimulus relative to the viewer determines the severity of neglect. Horizontal line bisection, for example, may be considered an object-centred task given that the bisection error (LBE) correlates with the extent of the neglected letter string of single words in neglect dyslexia (Reinhart et al., 2013), and covaries with line length (Halligan and Marshall, 1991). On the other hand, LBE has also been found to vary relative to the viewer (Utz et al., 2011a, i.e. in the Schenkenberg test) and to correlate positively with search

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and reading biases in cancellation tasks as well as paragraph reading (Reinhart et al., 2013).

On a neural level, ego- and object-centred visual processing seem to recruit different brain structures (Olson and Gettner, 1996): Single-cell recordings in monkeys have identified neurons in the frontal cortex (Olson and Gettner, 1995) that discharge selectively when the allocation of attention to the contralateral part of a perceptual object is required. This contrasts with the properties of neurons in the monkey parietal cortex, where neurons discharge when the allocation of attention to regions in contralateral space is required (Gottlieb, 2002). In a recent study, Benwell et al. (2014) found an association between the leftward line bisection error in healthy participants (pseudo neglect; Jewell and McCourt, 2000) and the right hemisphere ventral attention network, in particular areas of the right parietal cortex around the temporo-parietal junction. Functional imaging studies in healthy humans yielded similar findings of differential activations associated with ego- and object-centred space processing (Honda et al., 1999; Vallar et al., 1999): object-centred visual processing was found to be mostly related to activations in the temporal and – to a smaller extent – in the frontal cortex. Egocentric visual processing, on the other hand, has been associated with activations in the parietal and – to a lesser degree – in the frontal cortex (Vallar et al., 1999). Finally, studies in neuropsychological patients show a similar picture: Hillis et al. (2005) observed object-centred visual neglect phenomena in a cancellation task in patients with lesions of the right superior temporal gyrus, but egocentric errors (omissions) in the same task in patients with damage of the right angular gyrus. Put differently, egocentric visual neglect phenomena are mostly linked to the dorsal visual stream (parieto-frontal cortices) while object-centred visual neglect phenomena are more associated with ventral stream lesions, in particular the temporal lobe (Grimsen et al., 2008; Ptak and Valenza, 2005).

Electrical stimulation of the vestibular system can be induced by placing one electrode behind each ear over the left and right mastoid respectively (termed galvanic vestibular stimulation or GVS, for review see Utz et al., 2010). Underneath the mastoids the vestibular nerve projects from the inner ear to the vestibular brain stem nuclei, which in turn are interconnected with the nucleus ventroposterolateralis of the thalamus. From there, ascending vestibular fibre pathways reach a number of cortical vestibular areas including area 2cv near the central sulcus, area 3a,b in the somatosensory cortex, parietal area 7a, and the parieto-insular-vestibular-cortex (PIVC). Although there is no primary vestibular cortex as for the visual-, auditory- or tactile modality, the above mentioned array of multiple, interconnected vestibular cortical areas is thought to be under the control of the PIVC (Guldin and Grusser, 1998). Practically, GVS consists of applying direct current to the mastoids – usually delivered by a small battery-driven constant current stimulator (Wilkinson et al., 2008). Subliminal GVS can be administered by adjusting the current intensity below an individual's sensory threshold. This has the methodological advantage that different GVS protocols and polarities can be manipulated elegantly without the patient's knowledge that might otherwise influence his performance due to “spatial cueing” effects induced by a tingling sensation under one electrode. Furthermore, GVS is painless, easily applicable, safe, and induces minimal side effects when used in accordance with standard safety guidelines (Utz et al., 2011b).

GVS has significant effects on a wide variety of cognitive and perceptual tasks, both in healthy persons and neurological patients (for review see Utz et al., 2010). For example, Wilkinson and co-workers found that GVS facilitated visual memory recall in healthy participants (Wilkinson et al., 2008) and improved visuoconstructive deficits in a right-hemisphere lesioned patient (Wilkinson et al., 2010). A recent study by Wilkinson et al. (2012) found significant effects of GVS on an electrophysiological component (N170) in a face processing task. This underlines the physiological effects of GVS in modulating neuronal activity in visual areas of the ventral stream. Moreover, a few sessions of GVS were shown to induce a lasting treatment effect in visuospatial neglect (Wilkinson et al., 2014). Furthermore, Saj et al. (2006) demonstrated a positive effect of CL/AR GVS on the perceptual tilt of the subjective vertical in right-hemisphere lesioned patients with left neglect. In addition, Kerkhoff et al. (2011) and Schmidt et al. (2013b) found a long-lasting beneficial effect after 3 verum sessions of CL/AR and AL/CR GVS in tactile extinction. Finally, Utz et al. (2011a) showed a significant improvement in line bisection (Schenkenberg test) after AL/CR and partially also after CL/AR GVS in 6 patients with left visuospatial neglect, but no effect in 11 right-hemisphere stroke patients without neglect.

In summary, there is increasing evidence that GVS can significantly modulate a range of cognitive capacities or impairments in both healthy persons and neurological patients (partially with neglect). So far, it is not known whether the modulatory effect of GVS on neglect is restricted to egocentric space processing such as observed in cancellation tasks (Rorsman et al., 1999) or whether it has also the capacity to influence additional components of impaired space processing such as object-centred neglect. As the brain areas associated with object-centred visual attention (Honda et al., 1999) are remote from those typically activated by GVS (Bense et al., 2001) it is unclear whether their activity can be modulated by GVS. From both, a theoretical and a clinical viewpoint, it would be important to know whether galvanic vestibular stimulation modulates not only egocentric but also object-centred components of visual neglect. Clinically, this is clearly relevant as neglect patients are typically impaired in both spatial components of visual neglect and therefore require specific rehabilitation techniques for intervention. Moreover, while egocentric neglect phenomena can be treated by a variety of novel therapies (for review see Kerkhoff and Schenk, 2012) no treatment is currently available for object-centred neglect, to the best of our knowledge. Theoretically, a potential vestibular influence on these different components is also interesting, as it may clarify the relationship between mechanisms of visual attention operating in ego- vs. object centred coordinate systems and the cortical vestibular system (Grimsen et al., 2008; Olson and Gettner, 1996). Hence, the aim of the present study was to investigate whether subliminal GVS modulates ego- and object-centred spatial processing components of visual neglect significantly.

2. Patients and methods

2.1. Patients and healthy controls

The study – which was approved by the local ethics committee (Ärztekammer des Saarlandes, Nr. 147/08, 16.9.2008) – included 24 patients with unilateral right-sided stroke (Table 1). Inclusion criteria were right-handedness and a single right hemisphere infarction or haemorrhage. Exclusion criteria were other neurological or psychiatric diseases, epilepsy, sensitive skin on the scalp, metallic brain implants and medications altering the level of cortical excitability (Iyer et al., 2005). The participants were 10 women and 14 men with a median age of 63.6 years (range 42–84 years), and a median time since lesion of 2 months (range: 1–84 months). For each of the four neglect tasks described below the patients were – depending on their performance in the sham-baseline condition – allocated to a patient group *with neglect* (RBD+) in a specific task or a patient group *without neglect* (RBD−) in that task.

In addition, 28 healthy, age-matched controls (11 male, 17 female, median age: 56 years (range: 44–75 years) were tested to collect normative data for these tasks. This was achieved by establishing cut-off criteria for assigning patients to the RBD− or RBD+ groups. The healthy controls did not participate in the experimental (stimulation) sessions.

2.2. Experimental procedures

In the first session all participants performed the four tasks while the electrodes of the stimulation device were fixed over the mastoids but not active