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Body representation disorders predict left right orientation impairments after stroke: A voxel-based lesion symptom mapping study

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ABSTRACT

Introduction: Deficits in the ability to distinguish between the left and right side of the body can severely impair daily life functioning. The current study examined the relation between left right orientation (LRO) impairments and somatosensory related deficits, ranging from primary somatosensory impairments to body representation impairments, in patients who suffered a recent stroke. We also examined which areas in the brain are associated with LRO impairments using a Voxel-based Lesion Symptom Mapping (VLSM) analysis.

Method: We tested 47 first-ever stroke patients and 48 age-matched healthy controls. LRO was assessed with the Bergen Right Left Discrimination Test (BRLD). Impairments on primary somatosensory function (touch perception, proprioception), higher order somatosensory function (finger gnosis, subjective sense of body ownership) and other cognitive functions (language, attention & working memory, visuospatial neglect) were entered as predictors in a logistic regression analyses. Outcome measures consisted of the BRLD-total performance which was further subdivided in performance for 1) first person perspective stimuli, 2) third person perspective stimuli, 3) alternating between first- and third person perspective.

Results: Impairments on BRLD-total performance was predicted by impairments in finger gnosis and visuospatial neglect. For items placed in third person perspective, performance was predicted by body representation impairments; finger agnosia and the subjective sense of body ownership. VLSM analysis showed a significant association between LRO impairments and damage to the right insula.

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Discussion: The current study suggests that the somatosensory system is important for LRO. Furthermore, the results indicate that an affected body representation may hinder adopting a third person perspective that may subsequently also lead to LRO impairments. The right insular cortex appeared crucially involved in these processes.

1. Introduction

In daily life the ability to distinguish left from right is of profound importance for orientation and navigation. It requires awareness that the left and right side of our body are different and it requires the ability to verbally name the terms 'left' and 'right' (Mendoza & Foundas, 2007). As such, impairments in left right orientation (LRO) can be caused by multiple factors, such as impairments in language, spatial mapping (Gold, Adair, Jacobs, & Heilman, 1995), and higher order aspects of the somatosensory system, such as body representation deficits (Benton, 1959). Several different body representations have been described (Gallagher, 2005; Paillard, 1999; de Vignemont, 2010), such as action related representations, structural representations and spatial body representations (Head & Holmes, 1911; Schwoebel & Coslett, 2005). A deficit in body representation may result in problems in identifying body parts, such as the fingers in finger agnosia. Indeed, finger agnosia has been related to LRO impairments and is, together with acalculia and agraphia, described as the Gerstmann syndrome which is associated with lesions in the left parietal lobe (Gerstmann, 1940). Other studies have related LRO to more spatial functions, primarily mediated by the right hemisphere. That is, spatial information is especially important in left-right decisions when mental rotation of the object is required (Ditunno & Mann, 1990; Harris, Harris, & Caine, 2002; Ratcliff, 1979). Mental rotation requires the ability to mentally manipulate (turn, twist or rotate) an image in order to match it to another image (Shepard & Metzler, 1971). In a study of Ratcliff and colleagues (Ratcliff, 1979), brain injured patients performed a LRO task with and without requirement of mental rotation. Results showed that patients with left parietal lesions made more errors than patients with right parietal lesions when the stimuli where presented in a first person perspective whereas this was the other way around if the stimuli had to be mentally rotated. In line with these results, Harris and colleagues (Harris et al., 2002) presented a case study in which the right basal ganglia lesion resulted in LRO problems when the stimuli were presented in an allocentric reference frame (third person perspective), but not when presented in an egocentric reference frame (first person perspective). Thus, LRO for stimuli that need mental rotation seems to involve visuospatial abilities mediated by the right hemisphere.

There is evidence that not only visuospatial function, but also body related signals are important when stimuli are positioned in a third person perspective. Several studies found activation in brain areas involved in motor execution and planning when stimuli had to be mentally rotated to align the stimuli with the egocentric reference frame. For example, in laterality judgements tasks, participants are asked to identify the left or right hand of a line drawing (Parsons, 1987; Sekiyama, 1982). Participants mentally rotate their own hand into the stimulus's orientation to enable matching which demands input from the body related motor system. In turn, impairments of the motor system might affect performance on LRO tasks. For example, upper limb amputees' performance on a LRO is affected by the side of limb loss (Nico et al., 2004). That is, amputation of the dominant hand results in stronger LRO problems than amputation of the non-dominant hand. Similarly, individuals with congenital limb absence (Funk & Brugger, 2008), writer's cramp patients (Fiorio, Tinazzi, & Aglioti, 2006) and chronic pain patients (Coslett, Medina, Kliot, & Burkey, 2010; Moseley, 2004; Schwoebel, Friedman, Duda, & Coslett, 2001) show problems in deciding whether a corporeal stimulus is left or right, suggesting that afferent bodily signals are of paramount importance for LRO.

Yet, it is not clear which information of the body is crucial, this may vary from primary somatosensory and motor information to higher order representation of the body. Furthermore, it is not clear whether bodily information is important for stimuli viewed from a first person, from a third person, or from both perspectives. We aimed to investigate whether LRO with and without mental rotation can be selectively impaired after stroke. In addition, we investigated whether somatosensory (from primary to higher order) representations are related to impairments on LRO with and without mental rotation. Next, we performed a voxel-based lesion symptom mapping (VLSM) analysis. This analysis was conducted in a part of the sample, and was exploratory and assumption-free in nature, meaning that involvement of regions anywhere in the brain was assessed. By doing so, we aimed to assess the anatomical correlates of LRO, and to compare the anatomical substrate between the different subtests of the BRLD Test.

2. Methods

2.1. Patients

Patients with a unilateral first-ever supratentorial stroke were included. They met the following criteria: i) age of 18 years or older and admitted to the stroke unit of the Academic Hospital, ii) no other neurological or psychiatric condition apart from the stroke, iii) ability to communicate in Dutch, iv) no prior cognitive disorders that could hamper the validity of the test performance on the BRLD (for example, the diagnosis of a dementia, delirium or a depression). All patients had to be able

participate in a neuropsychological examination for a minimum of 1 h.

Diagnosis of a stroke was based on a clinical examination of a neurologist and was confirmed with CT-scanning or MR-imaging. During hospital stay, patients underwent a neuropsychological examination that included tests aiming at the somatosensory and body representation function and tests that measured attention & working memory, language and visuospatial neglect. The tests were conducted within 3 weeks post stroke. The neuropsychological examination was a part of standard work at the stroke unit (see Neuropsychological examination).

2.2. Healthy controls

See Table 1 for characteristics of the participants. Controls had no prior neurological disease nor were there indications of cognitive dysfunctions. Participants were recruited through advertisement and received a financial compensation. The neuropsychological examination was similar to the one that was conducted in the stroke patients. The experiment was performed in accordance with the declaration of Helsinki, and the protocol was deemed to be without psychological or medical risks, and complied with good ethical standards by the ethical advisory committee of the Faculty of Social and Behavioral Sciences at Utrecht University.

2.3. Neuropsychological examination

2.3.1. Left right orientation

We used the Bergen Right Left Discrimination Test (BRLD) to assess LRO (Ofte & Hugdahl, 2002). This is a test that has been commonly administered in experimental settings and consists of stickmen in different views of reference of which a participant has to indicate what the left or right hand of the stickmen is. It has been suggested that the subversions of the test measure LRO with and without mental rotation (Grewe, Ohmann, Markowitsch, & Piefke, 2014; Jordan, Wüstenberg, Jaspers-Feyer, Fellbrich, & Peters, 2006). The three conditions of the BRLD contain line drawings of stickmen, with two arms and a triangle that indicate the shoulders (see Fig. 1). Stimuli consisted of stickmen that were either viewed from the back (first person perspective), the front (third person perspective) or alternating between back and front. Participants had to mark either the left or the right hand of each stickman, depending on the letter L or R that was printed below the stickman. Stickmen viewed from the front are regarded as stimuli that need mental rotation. That is, in order to determine what the left or right hand is, the participant need to either mentally rotate the image or make a shift from a first person to a third person perspective (Grewe et al., 2014). There are 48 figures in each subtest. The arms of the figures are drawn at different angles and positions related to its body. That is, arms are uncrossed, one arm crosses the vertical axis of the stickmen, or 2 arms cross the vertical axis of the stickmen. There are equal numbers of each arm position in the test. The participants had to mark as many stickmen as possible within 90 s. For the exact procedure see Ofte (2002). The primary outcome measure was an accuracy score, consisting of the percentage of correctly marked stickmen. The accuracy score was calculated for the three conditions, i.e., BRLD-Back, BRLD-Front and BRLD- Alternating. A BRLD-total score was calculated as the sum score of the three conditions.

Table 1 – Characteristics of patients and healthy controls.

	Patients	Healthy controls
N	47	48
Male (%)	25 (53.2%)	22 (45.8%)
Age *year* ±*SD*	61.5 ± 15.5	61.2 ± 9.0
Handedness (right)	42 (89%)	38 (79.2%)
Education (*level* ±*SD*)	4.9 ± 1.0	4.7 ± 1.4

Education levels categorised based on Verhage (1964), a Dutch classification system including 7 categories. 1 = did not finish primary school, 2 = finished primary school, 3 = did not finish secondary school, 4 = finished secondary school, low level, 5 = finished secondary school, medium level, 6 = finished secondary school, highest level, and/or college degree, 7 = university degree.

2.3.2. Predictors

The following 13 variables were a priori selected as predictors of BRLD performance. First, patient characteristics consisted of 1) gender, 2) handedness, 3) education and 4) affected hemisphere (stroke in left or right hemisphere) and 5) type of stroke (ischemic or haemorrhagic). Second, behavioural outcome measures of somatosensory function and body representation function were selected. Two questions concerning the subjective experience of somatosensory dysfunctions were included. That is, 6) whether the patient noticed problems in touch perception as a result of the stroke, i.e., "Did you experience difficulties in the perception of touch? (y/n)". The other question concerned whether the patient noticed problems regarding the subjective sense of body ownership, i.e., 7) "Have you experienced the feeling that one of your limbs did not belong to yourself? (y/n)". And if so, patients are asked which of the limbs(s) it concerns. For all patients who reported ownership problems, it related to the contralesional arm. In case patients did not fully understand the meaning of the question, the trained neuropsychologist provided additional information on touch perception and subjective sense of body ownership. Next, somatosensory functioning was examined by objective measures for the primary somatosensory function. That is, 8) touch perception and 9) proprioception. Touch perception was examined by administering 1 or 2 tactile stimuli on the fingers. Patients had to respond on how many stimuli (1 or 2) were felt (7 trials each hand, 14 in total). Proprioception was examined based on the proprioception subtest of The Rivermead Assessment of Somatosensory Performance (Winward, Halligan, & Wade, 2002) i.e., the direction proprioception of the thumb (10 movements for each thumb, 20 in total). Information on the structural body representation was measured by 10) finger gnosis. To examine finger gnosis, patients were asked to name the finger that had been touched, while blindfolded (7 trials each hand, 14 in total). Patients with bilateral primary somatosensory deficits (touch perception) did not perform the finger gnosis task. Patients with unilateral deficits were tested on the other ('unaffected') hand since finger agnosia has been regarded as a

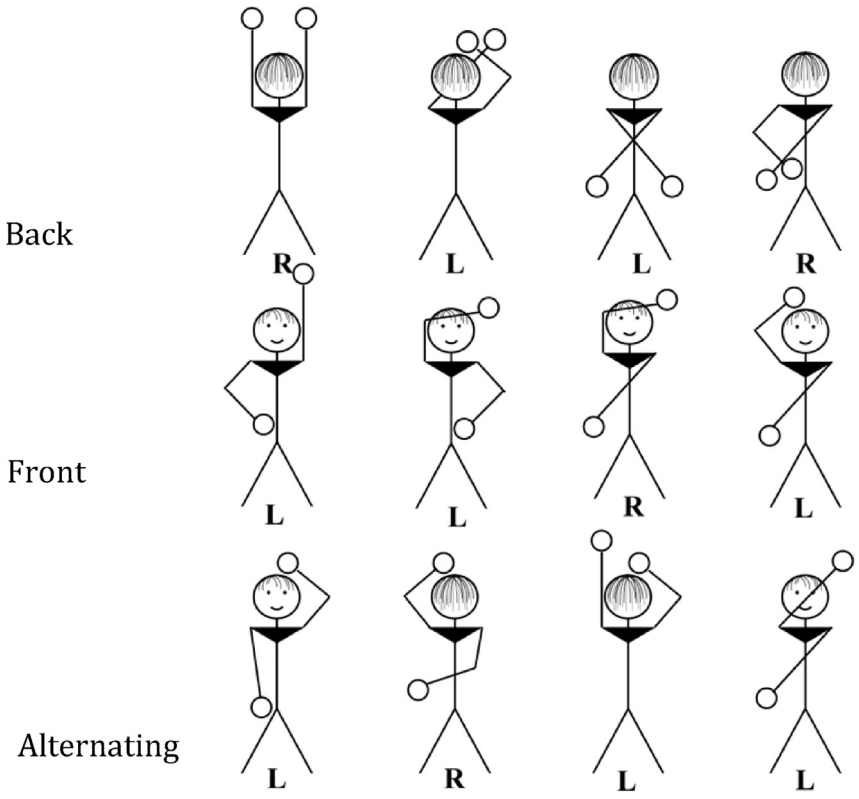

Fig. 1 – Stimuli of the BRLD test. Example of items of the BRLD test with three subtests: Back stimuli (first-person view), Front stimuli (third-person view) and Alternating stimuli. Each subtest was administered for 90 s; the outcome measure was based on the percentage correct score. In case the percentage correct score was 2SD below the mean, the performance was regarded as impaired. The BRLD-total score was the average score of all three conditions.

disorder that is bilaterally presented (Lezak, 2004). Apart from predictors within the somatosensory and body representation domain, three tests aiming at other cognitive functions were included as well. First, language deficits are known to influence BRLD task performance since patients ought to discriminate between the letters L and R. Therefore, 11) language impairments were examined by the Boston Naming Task (Saxton et al., 2010). Next 12) attentional span and working memory, a function susceptible for cognitive harm, was examined by the digit span (back- and forward) of the Wechsler Adult Intelligence Scale III (Dutch condition) (Wechsler, 1987). Finally, 13) visuospatial neglect was measured by the Star Cancellation Test (Halligan, Cockburn, & Wilson, 1991). Outcomes were transformed to categorical variables by setting a cut-off (impaired or unimpaired) (see Table 2).

2.4. Analyses

2.4.1. Neuropsychological examination

BRLD test performances of patients were transformed into z-scores based on the scores of the healthy control group. Patients performing with a z-score ≤ -2 were labelled as impaired. As such, patients were divided in two groups, i.e.,

Table 2 – Results of BRLD test.

	Healthy Controls		Patients		Cut-off for impaired performance
	Number of marked stickmen (mean ± SD)	Percentage correct (mean ± SD)	Number of marked stickmen (mean ± SD)	Percentage correct (mean ± SD)	Percentage correct
BRLD-total	96.5 ± 14.9	94.79 ± 7.22	56.49 ± 21.26	84.41 ± 15.87	80.35%
BRLD-back	34 ± 5.66	95.12 ± 8.10	21.72 ± 8.0	86.17 ± 16.65	78.92%
BRLD-front	32.40 ± 6.18	94.61 ± 8.00	19.2 ± 8.48	84.79 ± 21.10	78.61%
BRLD-alternating	30.13 ± 5.42	94.29 ± 8.66	16.83 ± 6.87	81.64 ± 18.95	76.97%

Numbers represent the absolute scores of the 4 outcome measures of the BRLD test for patients and healthy controls. Based on the healthy controls group, z-scores were formed and a cut-off was set for the percentage correct on 2 SD below the control mean.

impaired and unimpaired. For BRLD performance, the outcome measure was the percentage correct score, that is number of correctly marked stickmen, divided by the total amount (correct + incorrect) stickmen. Patients had to mark a minimum of 5 items for the back condition, 3 items for the front condition and 3 items for the alternating condition in order to be included for analyses. This minimum total number of marked stickmen was set on 2SD below the mean of the performance of the patients. To analyse whether a difference exists between the patients and healthy controls on participant characteristics, a one-way ANOVA was conducted on age and educational level. For handedness, gender, side of stroke and type of stroke, the non parametric chi square test was conducted. To test whether a difference exists between the conditions (total, back, front and alternating), a mixed design ANOVA was conducted, with group (patients and controls) as a between subjects factor A forward logistic regression analysis was performed to examine the relationship between the BRLD test and the 13 predictors. Analyses were conducted for the BRLD-total score, BRLD-back, BRLD-front and BRLD-alternating condition. Outcome measures of the BRLD test as well as the 13 predictors were categorical, i.e., impaired or unimpaired (based on de z-scores). The predictors were entered into the model with a forward selection (LR) with a p value set on <.05. To test whether the patients included for VLSM analyses differed from the excluded patients, a one-way ANOVA was conducted on age and educational level. For handedness, gender, educational level, side of stroke and type of stroke, the non parametric chi square test was conducted. Next, the logistic regression was repeated for the VLSM-group only, to verify if the behavioural results were in line with those of the total patient group.

2.4.2. *Voxel-based lesion symptom mapping*

For the exact procedure on VLSM procedure, see Biesbroek et al. (2014) and Brink et al. (2016). In short, lesion maps were generated by manually delineating the lesion on either a CT of MRI scan by one reviewer who was blinded to neuropsychological data (JMB). The lesion maps were registered to the T1 MNI-152 (Montreal Neurological Institute) template (Fonov, Evans, McKinstry, Almli, & Collins, 2009). MRI scans were registered using elastix (Klein, Staring, Murphy, Viergever, & Pluim, 2010); CT scans were registered using a registration algorithm that was designed and validated for this purpose (Kuijf, Biesbroek, Viergever, Biessels, & Vincken, 2013). An intermediate CT/MRI template was used to enhance the quality of the registration procedure (Rorden, Bonilha, Fridriksson, Bender, & Karnath, 2012). Quality checks were performed by comparing the original scan to the lesion map in MNI space by one reviewer who was again blinded to neuropsychological data and made manual adjustments if necessary (JMB). The procedure resulted in an accurate translation of the lesion maps to standard space in all cases. Regarding the statistics, VLSM analyses were performed with Non-parametric mapping (version December 2015, settings: Liebermeister) (Rorden, Bonilha, & Nichols, 2007). Four (binary) dependent variables were specified; impairments (y/n) on the BRLD total, back, front and alternating test. Voxels affected by ischemic lesions in less than 3 patients were not considered for analysis. Correction for multiple testing was achieved using the conservative Bonferroni familywise error correction (p < .05).

2.4.3. *Region of interest-based analyses*

To quantify the impact of regional lesion volumes, a Region of Interest (ROI)-based analysis was conducted. For this purpose, 96 cortical and 21 subcortical non-overlapping regions were extracted from the probabilistic Harvard–Oxford atlas (threshold at .25) (Desikan et al., 2006). Regions for subdivisions of gyri were merged into a single variable, thereby reducing the total number of regions to 89. For an elaborate description of this procedure, see Brink et al. (2016). An assumption-free approach was applied, meaning ROI's were not pre-selected beforehand. Instead, lesion volumes for all 89 ROI's were entered as independent variables in a Forward selection stepwise logistic regression model with the 4 binary outcome measures (impaired performance (y/n) on BRLD-total, BRLD-back, BRLD-front and BRLD-alternating) as dependent variables. The predictors were entered into the model with a p value set on <.05.

3. Results

The majority of the patients suffered from an ischemic stroke (42 patient, 89%), and 5 patients suffered from a hemorrhagic stroke. Of all patients, 24 (51%) had lesions in

Table 3 – Impairments on the BRLD subtests.

Percentages of impairments on three conditions		BRLD-alternating					
BRLD-back		Unimpaired		Impaired		Total	
Unimpaired	BRLD-front	28	59.6%	8	17.0%	36	76.6%
	Unimpaired	25	53.2%	4	8.5%	29	61.7%
	Impaired	3	6.4%	4	8.5%	7	14.9%
Impaired		4	8.5%	7	14.9%	11	23.4%
	Unimpaired	4	8.5%	1	2.1%	5	10.6%
	Impaired	–	–	6	12.8%	6	12.8%
Total		32	68.1%	15	31.9%	47	100.0%

Cross table that show the percentages of impairments within the patient group on the three condition of the BRLD task. Impairments were based on the healthy control group (2SD below the mean). Impairments were most frequent on the BRLD-alternating condition (31.9% of the patients) followed by the BRLD-front condition. Note that patients could be impaired on the BRLD-back but not on the BRLD-front or vice versa.

the right hemisphere. Patients were on average 61.5 years old (SD 15.5 years). For patient characteristics, see Tables 1 and 4. In 32 patients, a MRI or CT scans were found to be suitable for a Voxel-Based Lesion Symptom mapping (VLSM) analyses. See VLSM analyses for more details. For the distribution of raw accuracy scores for the BRLD total performance of healthy participants and patients, see Fig. 2. For average number of crossed stickmen and percentages correct, see Table 2. Six patients did not complete all tests and were therefore excluded from the regression analyses. For BRLD-total performance, healthy control subjects scored an average of 94.8% (±7.2) correct. For stroke patients, the average BRLD-total score was 84.4% correct (±15.9) Stroke patients showed an average accuracy of 86.6% on the BRLD-back condition, 84.8% on the BRLD-front and 81.6% in the BRLD-alternating condition. Patients performed significantly worse than control subjects on percentages correct F (1, 93) = 1,43 $p < .05$ but no differences between the subtests appear to be significant.

3.1. BRLD impairments

For the BRLD-total score, 13 out of 47 patients were found to be impaired (28%) (see Table 3). Zooming in on the three conditions, 25 patients (53.2%) were unimpaired for all three conditions. Six patients (12.8%) were impaired for all three conditions. 11 patients (23.4%) were impaired on BRLD-back, of whom 10.6% (5 patients) were unimpaired on the BRLD-front and 8.5% (4 patients) were unimpaired on the BRLD-alternating task. For patients who were impaired on the BRLD-front, only 3 patients (6.4%) were unimpaired on the BRLD-alternating. Of the 15 patients that were impaired in the BRLD-alternating, 5 were unimpaired on the BRLD-front task. See Table 3 and Fig. 2 for all details.

3.2. Behavioural predictors

3.2.1. BRLD-total

Logistic regression found that finger agnosia contributed significantly to BRLD-total performance. That is, patients who showed impairments on the finger gnosis task were significantly more impaired on BRLD-total than patients without finger gnosis deficits, B 2.95, Exp (B) .54 $p < .02$ (see also Fig. 3). Regarding the other cognitive functions, visuospatial neglect significantly contributed to BRLD-total performance B 3.44, Exp (B) .32 $p < .01$. That is, patients suffering from neglect showed more incorrect items on the BRLD-total performance as opposed to patients without neglect.

3.2.2. BRLD-back

Regarding the BRLD-back percentage correct; visuospatial neglect predicted performance strongest B 2.78, Exp (B) .062 $p < .01$. Taking neglect out of the model, BRLD-back performance was strongest predicted by subjective touch impairment B 1.946, Exp (B) 1.43 $p < .05$. That is, patients who reported problems in touch perception performed worse than patients who did not report touch perception impairments. None of the other predictors were related to BRLD-back performance.

3.2.3. BRLD-front

Regarding the BRLD-front percentage correct, subjective sense of body ownership impairments contributed to BRLD-front impairments B 3.22, Exp (B) .04 $p < .02$. That is, patients that reported body ownership deficits had a higher chance of showing impairments in BRLD-front task. In addition, finger agnosia significantly predicted BRLD-front impairments B 1.85, Exp (B) .16 $p < .05$. Visuospatial neglect trended towards significance B 2.18, Exp (B) .11 $p = .051$. None of the other predictors were related to BRLD-front performance.

3.2.4. BRLD-alternating

For BRLD-alternating performance, proprioceptive impairments predicted percentage correct impairments $B = 2.56$ Exp (B) .11 $p < .02$. In addition, gender was trending towards significance, meaning that women were less accurate than men $B = 1.69$ Exp (B) .19 $p = .06$. In order to assess which predictors were related to the switching between the front and back stimuli, the BRLD-alternating performance was corrected for the BRLD-back condition. For this score, attention and working memory was the only predictor that was found to be significant $B = 1.95$ Exp (B) .14 $p < .05$, suggesting that this predictor was related to the mental switching between back and front.

3.3. Neuroanatomical correlates (VLSM)

3.3.1. Behavioural data

The behavioural data as well as patient characteristics did not significantly differ between the whole group ($n = 47$) and the selected VLSM group ($n = 32$) which suggests that the VSLM subgroup is representative for the whole group. This concerned age, handedness, gender, educational level, side of stroke and type of stroke. Moreover, results of the regression analysis of the VLSM subgroup were in line with the total group, again suggesting that the VLSM subgroup was a representative sample of the whole group.

3.3.2. Lesion subtraction

Lesion overlay and subtraction plots of patients with impaired and unimpaired performance on the BRLD test are shown in Fig. 4. The right insula and right striatum were far more often affected in patients with impaired performance than unimpaired patients, suggesting a crucial role of these regions in left right orientation.

3.4. Voxel-based lesion-symptom mapping

VLSM analyses identified clusters of voxels with a statistically significant association between the presence of a lesion and BRLD impairments (Fig. 5). These voxels were mostly located in the right insular cortex. For the back and alternating subversions of the test, a similar pattern was found with significant voxels located predominantly in the right insular cortex. For the BRLD-front condition, none of the voxels were significantly associated with impairment after correction for multiple testing.

3.4.1. Region of interest-based stepwise regression analysis

For BRLD-total, BRLD-back and BRLD-alternating impairments, a statistically significant effect was found for the right

Table 4 – Characteristics of patient group for demographic and behavioural results. Each line represents each patient. The + indicates a positive results. That is, the first patients is included for VLSM analysis, suffers from subjective touch impairments, but not (–) from body ownership impairments. In addition, is does not show any impairments on the neuropsychological assessment nor on the BRLD test.

	Included for VLSM analysis	Age (years)	Gender	Educational level[a]	Affected hemisphere	Type of stroke	Handedness	Subjective touch impairments	Subjective body ownership impairments
1	+	70	f	6	r	ischaemia	r	+	–
2	+	37	m	5	l	ischaemia	r	–	–
3	+	56	f	4	l	ischaemia	r	–	–
4	+	63	f	3	l	ischaemia	r	+	–
5	+	84	m	5	l	ischaemia	l	–	–
6	+	57	m	6	l	ischaemia	r	–	–
7	+	66	m	5	r	ischaemia	r	–	–
8	+	54	m	5	r	ischaemia	r	+	–
9	+	48	f	4	r	ischaemia	r	+	–
10	+	76	f	4	l	ischaemia	r	–	–
11	+	75	f	x	x	ischaemia	x	–	–
12	–	84	f	5	r	ischaemia	r	–	–
13	+	79	f	6	l	ischaemia	r	–	–
14	+	46	m	5	l	ischaemia	r	+	–
15	+	66	m	7	r	ischaemia	r	–	–
16	–	84	m	2	r	ischaemia	r	–	–
17	–	78	f	5	r	ischaemia	r	+	+
18	+	49	m	6	l	ischaemia	r	+	–
19	+	61	m	6	r	ischaemia	r	–	–
20	+	56	m	6	r	ischaemia	r	–	–
21	+	48	f	4	l	ischaemia	r	–	–
22	–	69	m	6	l	ischaemia	r	+	–
23	+	64	f	5	r	ischaemia	l	–	–
24	+	49	f	5	r	ischaemia	r	–	–
25	+	69	m	4	l	ischaemia	r	–	–
26	+	69	f	3	r	ischaemia	r	–	+
27	–	72	f	4	l	ischaemia	r	+	+
28	+	46	f	4	l	ischaemia	r	+	–
29	–	33	m	6	l	ischaemia	r	+	–
30	+	66	m	5	l	ischaemia	r	–	–
31	–	55	m	4	r	hemorrhagic	r	+	–
32	–	80	m	5	r	ischaemia	r	–	–
33	–	49	f	5	r	hemorrhagic	r	+	+
34	–	85	f	5	r	hemorrhagic	r	+	–
35	–	49	m	5	r	ischaemia	r	–	–
36	+	71	m	5	l	ischaemia	l	–	–
37	–	87	f	5	l	ischaemia	r	–	x
38	+	83	m	5	l	ischaemia	r	–	–
39	–	27	m	5	r	hemorrhagic	r	+	+
40	+	48	f	3	r	ischaemia	r	–	–
41	+	58	m	6	l	ischaemia	r	+	–
42	+	43	f	6	r	ischaemia	l	+	–
43	–	41	f	5	l	ischaemia	r	+	–
44	–	46	m	5	l	hemorrhagic	r	–	–
45	+	75	m	4	l	ischaemia	l	–	–
46	+	74	f	7	r	ischaemia	r	–	–
47	+	45	m	4	r	ischaemia	r	+	+

insula cortex [BRLD-total $B = .847$ Exp (B) 2.33 $p < .01$, BRLD-back $B = .635$ Exp (B) 1.89 $p < .01$ and BRLD-alternating $B = .47$ Exp (B) 1.6 $p < .01$]. None of the remaining regions contributed to the model, nor did total infarct volume. For BRLD-front impairment, lesions within right insula cortex predicted performance as well $B = .506$ Exp (B) 1.658 $p < .01$, in addition to the left precentral gyrus $B = 1.52$ Exp (B) 4.55 $p < .05$.

4. Discussion

In the current study we aimed to elucidate the occurrence of left-right orientation (LRO) deficits shortly after stroke, it's predictors and neural correlates. We found that patients can be selectively impaired on different aspects of left-right

Visuospatial neglect	Language impairment	Attention & Working memory	Proprioception	Touch perception	Fingeragnosia	BRLD-total	BRLD-back	BRLD-front	BRLD-alternating
≥1 incorrect (lateralised)	Cut-off: <5th percentile	Cut-off: <5th percentile	Cut-off:: ≥1 incorrect	Cut-off: ≥1 incorrect	Cut-off:≥2 incorrect	Cut-off: <80.35% correct	Cut-off: <78.92% correct	Cut-off: <78.61% correct	Cut-off: <76.97% correct
–	–	–	–	–	–	–	–	–	
–	+	+	–	–	–	–	–	–	
–	–	–	–	–	–	–	–	–	
–	–	–	–	–	–	–	–	–	
–	–	+	–	–	+	–	–	+	
–	+	+	+	–	–	–	–	–	
+	–	–	+	–	+	+	+	+	
+	–	–	+	+	–	–	–	–	
–	–	–	+	–	+	+	+	–	
–	–	+	–	–	–	–	–	–	
+	x	x	+	–	–	+	+	–	
–	x	–	–	–	–	+	+	+	
–	+	–	–	–	–	–	–	–	
–	–	–	+	+	–	–	–	–	
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+	–	–	+	+	–	+	–	+	
x	–	–	–	–	+	+	+	+	
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+	–	–	+	+	–	+	+	+	
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x	–	–	–	+	x	–	–	–	
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x	–	–	–	–	–	–	–	–	
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–	+	+	+	–	–	+	–	+	
–	+	–	–	–	–	–	+	–	
–	–	+	+	–	+	+	–	–	
+	–	–	–	–	–	–	–	–	
+	–	–	+	+	–	+	+	+	

[a] Verhage, F. (1964). Intelligentie en leeftijd: Onderzoek bij nederlanders van twaalf tot zevenenzeventig jaar [Intelligence and age: Study with Dutch people from age 12 to 77]. Assen: Van Gorcum

orientation (LRO) since patterns of double dissociations between the subtests are found. That is, patient could be selectively impaired in LRO for stimuli placed in a first person perspective, a third person perspective or when switching between those two was required. Second, body representation impairments are a strong predictor of the total (sum) score of the test, as well as the subtest for third person perspective stimuli. Left right orientation in a first person perspective was

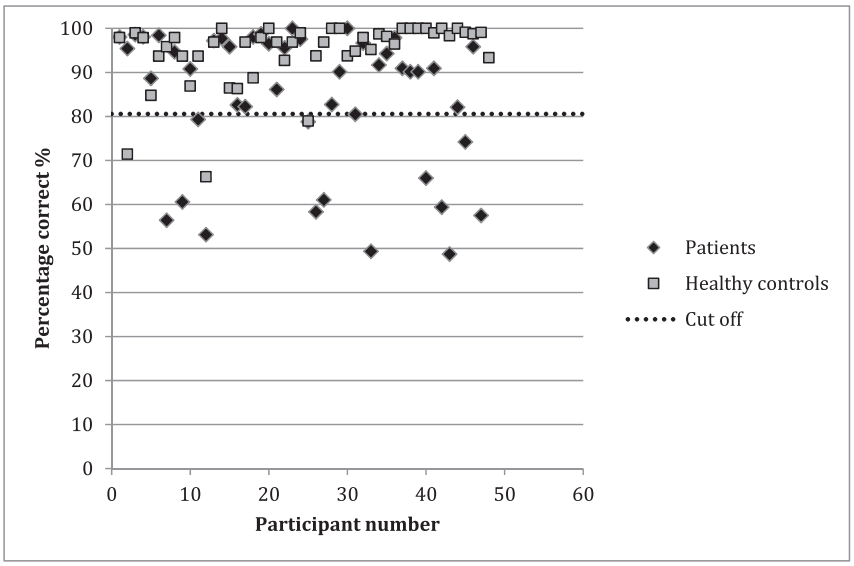

Fig. 2 – Results of BRLD scores per participant. Scores represent the BRLD-total percentage correct scores of patients ($n = 47$) and healthy controls HC ($N = 48$). The dotted line represents 2SD below the mean score of the HC. Patients below this line are regarded as impaired.

less strongly predicted by body representation deficits. Switching between first and third person perspective was predicted by proprioceptive impairments as well as attention and working memory. A third finding is that abnormalities of LRO are associated with lesions in the right insular cortex. This was found consistently across all conditions and was supported by a regression analysis that showed that lesion volume within the insular cortex was strongly associated with LRO impairments.

These three findings demonstrate a link between LRO, the somatosensory system and the insular cortex. This specifically shows that the higher order aspects of the somatosensory processing, those involved in body representation, are required to distinguish left from right. Previous studies have found that

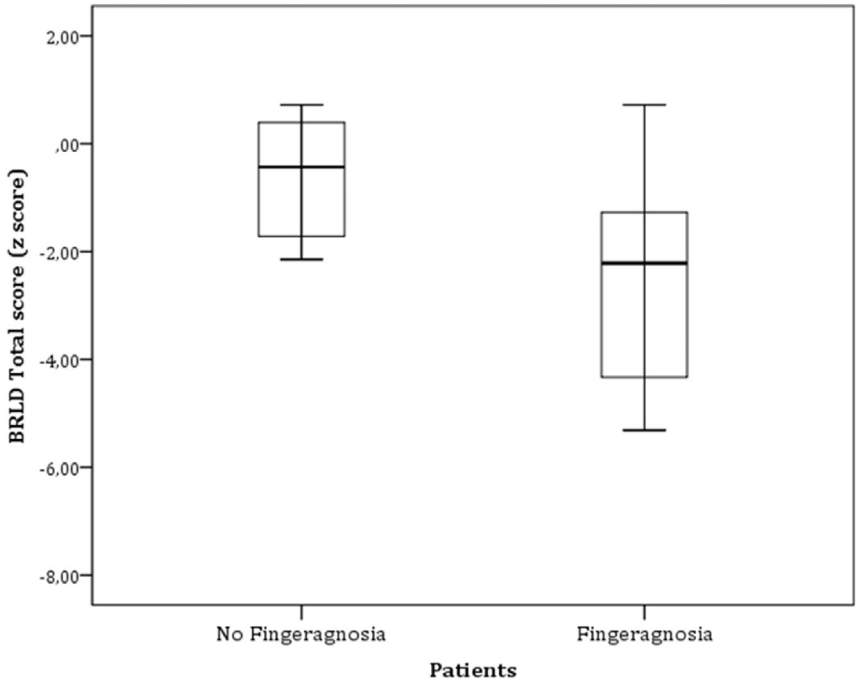

Fig. 3 – Results of BRLD total z-scores. Boxplot represents z-scores of BRLD-total test patients of patients with and without impairments on the fingergnosis test. Patients with an impairment on the finger gnosis test were likely to be impaired on the BRLD-total score.

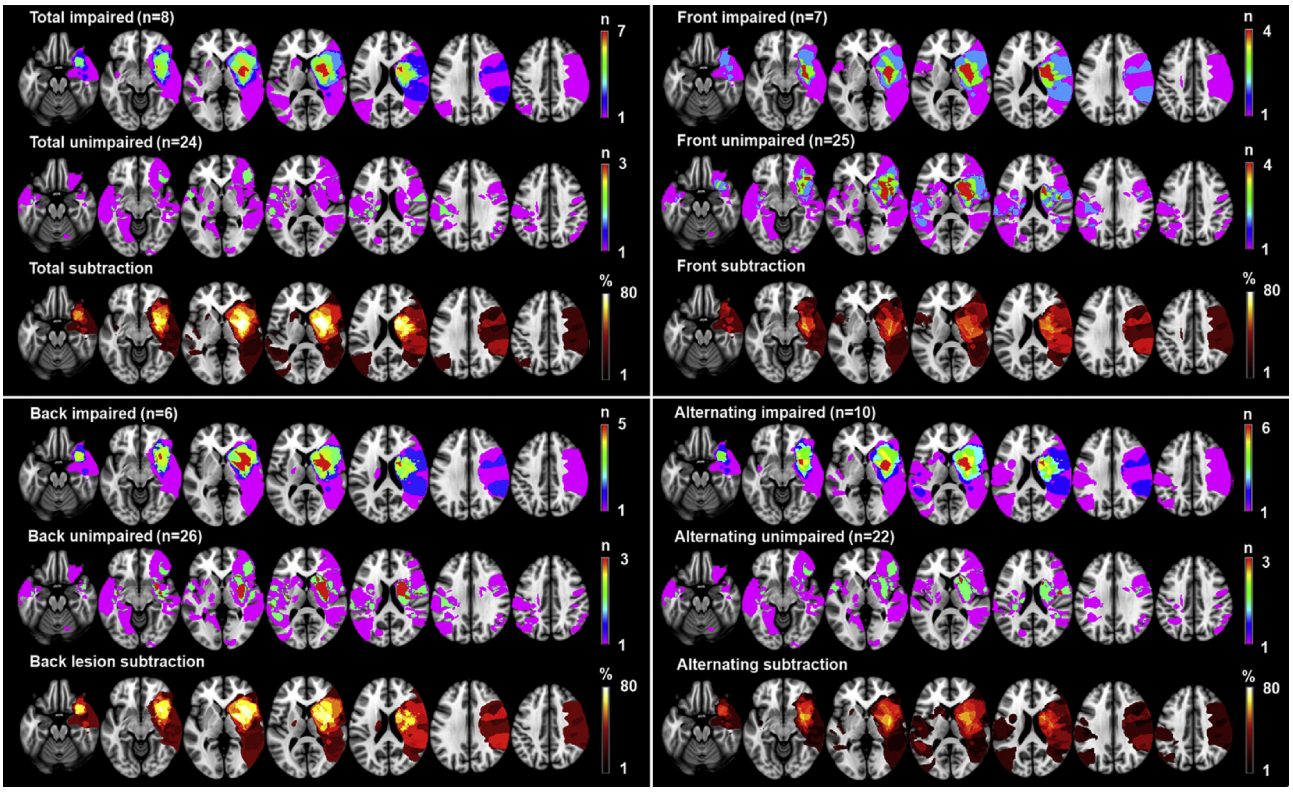

Fig. 4 – Lesion subtraction plot. Lesion subtraction plot of patients with impaired and unimpaired performance on the BRLD-total. In each box, the overlay plots (upper and middle rows) show the number of patients with a lesion for a given voxel separately for patients with impaired and unimpaired performance. The lesion subtraction plot shows which voxels are more often damaged in patients with impaired performance compared to patients with unimpaired performance (absolute difference in %). For example, the subtraction plot for BRLD-total performance shows that the absolute difference in lesion prevalence in the right striatum and insula is approximately 80% (with the insula and striatum being more often affected in patients with impaired performance).

primary sensorimotor functioning is important for LRO; these studies demonstrated that the sensorimotor function generates an update of the position of our own body or body parts, in order to match this information to the visual stimulus (Ionta & Blanke, 2009; Ionta, Fourkas, Fiorio, & Aglioti, 2007; Parsons, 1987; Shenton, Schwoebel, & Coslett, 2004). Our results suggest that higher order aspects of the somatosensory system are also involved in LRO. In the current study, body representation deficits consisted of structural body representation deficits (as measured by finger gnosis) as well as subjective body ownership deficits (as measured by subjective reports). Finger agnosia has been traditionally linked to LRO impairments in relation to Gerstmann syndrome. However, our study did not find a relation between finger agnosia and LRO per se, but only for stimuli in which a third person perspective has to be taken. In addition, subjective sense body ownership also showed a robust relation with LRO for third person perspective stimuli. A possible explanation would be that taking a third person perspective demands motor- and visual imagery (Brady, Maguinness, & Choisdealbha, 2011; Choisdealbha, Brady, & Maguinness, 2011; Conson, Mazzarella, Donnarumma, & Trojano, 2012) and this may be hindered by problems in recognizing or feeling your hand as your own. Taking a third person perspective requires a high cognitive demand as information from different modalities have to be integrated and translocated to another person's perspective (Blanke, Ortigue, Landis, & Seeck, 2002; Vogeley & Fink, 2003). Perhaps this process is hindered by impairments in higher order aspects of somatosensory processing which is exemplified by the deficits in finger gnosis and the subjective sense of body ownership complaints in the current study. This is in line with a recent study in stroke patients who suffer from body awareness problems (Besharati et al., 2016). This study investigated patients with and without anosognosia for hemiplegia (body awareness problems) on their ability to take a third person perspective. Results show that patients with anosognosia for hemiplegia exhibited more deficits in taking the third person perspective that positively correlated with the severity of body awareness. Other studies have found a link between body ownership and perspective taking as well. For example, symptoms of body ownership impairments were reduced when patients viewed one's affected arm through a conventional mirror (Fotopoulou et al., 2011; Jenkinson, Haggard, Ferreira, & Fotopoulou, 2013). Therefore, the body ownership impairments were only present when viewing the affected arm from a first person, and not a third person perspective. Although this study also demonstrates a link between body ownership and perspective taking, there are a few discrepancies with our current study. First, our patients who

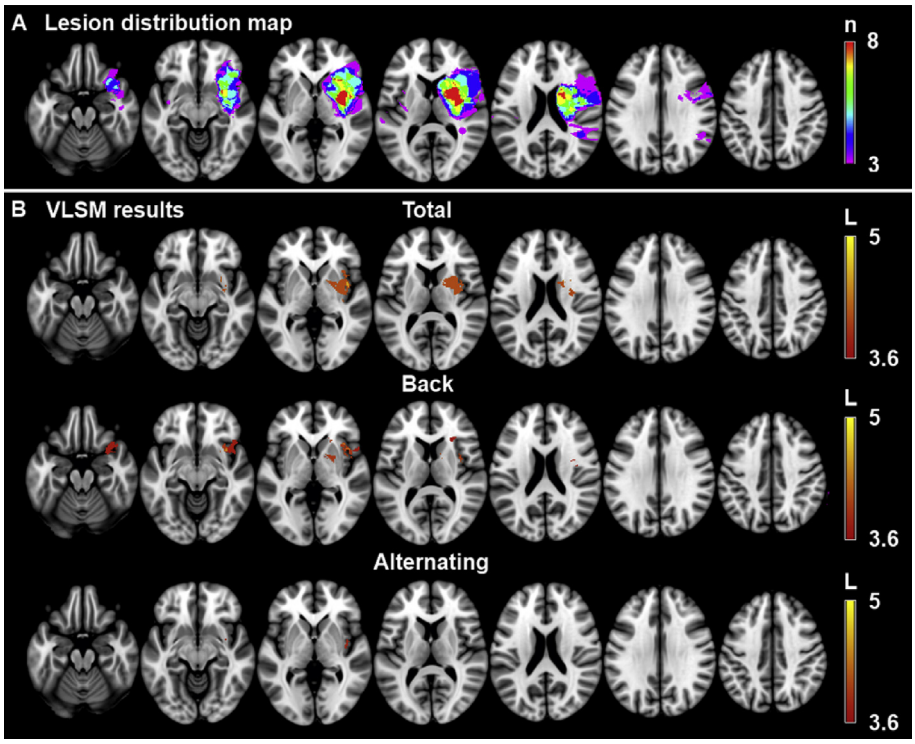

Fig. 5 – A) Lesion distribution map. Voxels that are damaged in at least three patients are projected on the 1 mm MNI-152 template. Colours indicate the number of patients with a lesion for each voxel. The majority of damaged voxels are located in the right hemisphere. B) Voxel based lesion symptom mapping results. Voxels with a statistically significant association (Liebermeister statistic) between the presence of a lesion and impairment on left right orientation tasks are shown on a scale from red to yellow. Results are corrected for multiple testing (Bonferroni FWE $p < .05$). For the BRLD-total, -back and -alternating condition, lesions in the right insula was associated with impairments, as can be appreciated from this figure. For the BRLD-front condition, no significant voxels were found.

reported problems in the sense of ownership did not all suffer from somatoparaphrenia as in the study of Fotopolou and colleagues (Fotopoulou et al., 2011; Jenkinson et al., 2013) in which a complete denial and rejection of ownership is present. In the current study, patients with body ownership problems were diagnosed when patients subjectively reported having problems in recognizing or feeling as if their hand belongs to themselves. Second, the study of Fotopoulou and colleagues showed that body ownership impairments are reduced by taking a third person perspective, while the current study show an opposite causal relationship, that is; taking a third person perspective is hindered when body ownership impairments are present. Together, these results suggest that perspective taking and body representation are tightly connected, but that the direction of their relation is equivocal. Another cue to the connection between spatial orientation and body representation comes from the finding that the right insula seems to be an important area to mediate these functions. An interesting line of research on this topic involves stimulation of vestibular input on spatial cognition and body representation (for review see Lopez, 2016). Caloric vestibular stimulation (CVS) or galvanic vestibular stimulation (GVS), stimulates the vestibular nerve through transcutaneous electrical current, while the head remains stationary. Stimulation of this network is associated with a wide range of sensorimotor as well as cognitive functions. Importantly, GVS reduces symptoms of visuospatial neglect and somatoparaphrenia (Bisiach, Rusconi, & Vallar, 1991; Rode et al., 1992; Salvato et al., 2016) as well as other body related disorders (Bottini, Gandola, Sedda, & Ferrè, 2013; Gandola et al., 2014; Lopez, 2016). Although the exact locations and functions of vestibular cortical areas are still a matter of debate, there is a wide agreement that the insular cortex plays a central role (Lopez & Blanke, 2011; Lopez, 2016). The current study may therefore reflect a similar mechanism in which the insular cortex is associated with body representation impairments as well as spatial (left right) orientation.

Three limitations of the current study should be mentioned. Our study population is probably not representative for the stroke population in general. Patients who could be examined for a minimum of 1 h within the first three weeks post stroke (average of 6 days) may be less affected by the stroke than the average stroke patient. Therefore, the prevalence of LRO impairments in this group might be an underestimation of the genuine prevalence in the population. Second, with regards to the notion that body representation deficits predict LRO impairments, one explanation for this relation might be that patients with somatosensory or body representation impairments are more affected by stroke in general, and are therefore also more impaired on other tasks such as the BRLD task. However, this explanation is not likely

for three reasons. First, the relationship between body representation and BRLD impairments only manifests in the BRLD-total, the BRLD-back and the BRLD-front conditions but is not apparent in the BRLD-alternating condition. As this latter condition is the most cognitively demanding subtask (Grewe et al., 2014), it is unlikely that this result is a function of severity of the stroke. Second, attention and working memory, a cognitive function susceptible for general cognitive harm, did not significantly correlate with body ownership impairment, nor did they significantly predict BRLD outcome except when isolating the switching component of the BRLD-alternating test. Third, ROI analysis did not find an association with total infarct volume and impaired performance. Therefore, somatosensory and body representation deficits might be genuinely modulating BRLD performance and not be explained by the severity of the stroke and its consequences.

A third limitation pertains to the VLSM analysis. The lesion frequency in the left cerebral hemisphere is relatively low (despite the substantial number of patients with left hemispheric lesions). One of the reasons is that patients with severe to global aphasia were not able to comprehend task instruction and the BRLD test was therefore not administered and patients were not included in the current study. As a consequence, most voxels in the left cerebral hemisphere were not included in the VLSM analysis. Therefore, we cannot draw any strong conclusions regarding the interhemispheric lateralization of LRO and body representation. Similarly, the lesion frequency of the posterior parts of the brain, including the occipital and posterior parts of the parietal cortex was low, which resulted in a low power to detect associations with LRO. Although the effect for the right insula was highly significant, this finding should be interpreted with caution. That is, the insula may not be the only area involved in LRO. Finally, the number of patients included for VLSM analyses was substantially lower than for the analysis of the behavioural data. This was largely due to the CT of MRI scan that was not suitable for analysis. However, the behavioural data as well as patient characteristics did not significantly differ between the whole group ($n = 47$) and the selected VLSM group ($n = 32$) that suggests that the VSLM group is representative for the whole group.

To conclude, the current study shows that LRO can be selectively impaired for stimuli in a first-person and third person perspective. Body representation impairments are associated with impairments in LRO for stimuli viewed from a third person perspective. Impairments with LRO are associated with lesions in the right insula cortex. These findings suggest that the right insular cortex may be involved in a network that represents both perspective taking and body representation.

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