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Thesis

Anatomy of body representation: Preliminary results

Neurological substrates of finger agnosia, left-right disorientation and the distinction between body image and body schema of the hand revealed using lesion-symptom mapping

David Sluiter
3680746
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First supervisor: Chris Dijkerman

Second supervisor: Haike van Stralen

VOORWOORD

Deze master thesis vormt de afsluiting van mijn Master Neuropsychologie aan de Universiteit Utrecht. In 2010 ben ik aan de bachelor Psychologie begonnen nadat ik in 2009 de HBO opleiding Fysiotherapie aan de Hogeschool Utrecht heb afgrond. Tijdens de bachelor Psychologie merkte ik dat de neuropsychologie het beste aansloot bij de zienswijze die ik als fysiotherapeut reeds ontwikkeld had: het diagnosticeren (dis)functioneel gedrag als gevolg van een disfunctie van het lichaam, in dit geval het brein, om deze vervolgens adequaat te behandelen. Ik heb deze thesis met plezier geschreven, omdat het onderwerp van deze thesis zowel aansluit bij mijn voorliefde voor motoriek als de werking van het brein. Het gaf mij de mogelijkheid mijn fysiotherapeutische kennis met mijn neuropsychologische kennis te verenigen.

Ik wil graag mijn eerste begeleider Chris Dijkerman bedanken voor zijn begeleiding. Zijn snelle, sturende antwoorden op mijn mails en de kritische kanttekeningen bij de uitvoer van het onderzoek hebben erg geholpen bij het schrijven van deze thesis. Ook wil ik mijn tweede begeleider Haike van Stralen bedanken voor de begeleiding. Haike, doordat de lesion symptom mapping approach ons beiden nieuw was, hebben we goed als team kunnen werken om ons deze methode eigen te maken. De relaxte sfeer tijdens onze samenwerking zorgde ervoor dat het alom gevreesde schrijven van de master thesis een ontspannen en vooral leuke bezigheid was. Ook wil ik Matthijs Biesbroek en Teuni ten Brink bedanken voor de uitleg en hulp bij het segmenteren en analyseren van de scans. Daarnaast wil ik alle participanten bedanken die hun vrijwillige medewerking aan het onderzoek hebben verleend.

ABSTRACT

Introduction

Body representation is a form of higher order somatosensory functioning containing multiple integrative processes in which information from different primary sensory modalities is integrated in a representation of the body. It is crucial for the conscious experience of the position and structure of our body parts and directing bodily movements. Disorders of body representation can affect the entire body or only specific body parts. The exact neurological substrate underlying body representation disorders remains unclear. The aim of the current study is to determine the neural substrate of body representation.

Methodology

In the present study we investigate in the neurological mechanisms underlying body representation-disorders in a sample of 17 first episode-stroke patients by linking neurological lesions with body representation disorders, i.e. finger agnosia, tactile localization impairments or left-right disorientation. Furthermore, the overlap and interplay between these impairments are mapped by using an advanced voxel-based lesion-symptom mapping approach.

Results

The voxel-based lesion-symptom mapping analysis showed that lesions significantly related to left right disorientation are mainly located in the right hemisphere, more specifically the caudate nucleus, external capsule and putamen. Analyses on finger agnosia and tactile localization impairments gained no significant results, but a qualitative lesion subtraction analysis shows a trend that lesions related to these disorders are also mainly situated in the right hemisphere, more specifically the caudate nucleus, external capsule , putamen and frontal cortex.

Conclusions

These results indicate that parts of the basal ganglia and the external capsule of the right hemisphere are key anatomical structures in body representation.

INTRODUCTION

An important function of the somatosensory system is informing us about the position of our body parts with respect to one another. In contrast to primary tactile functioning, this higher order somatosensory functioning contains multiple integrative processes in which information from different primary sensory modalities is integrated in a representation of the body. This so-called body representation is crucial for the conscious experience of the position and structure of our body parts and directing bodily movements.

Paillard (1999) and Gallagher (2005) described the presence of multiple representations of the body and that a distinction between these representations can be made between the *body image* and *body schema*. The body image refers to a conscious perceptual experience of body features. It is more visually based and is influenced by stored knowledge about the body structure and semantics. The body schema can be described as the unconscious representation of the position of our different body parts relatively to each other and surrounding space.
It is based on an integration of visual, vestibular, proprioceptive and tactile input, a mental framework which is continuously updated by our bodily movements and positional changes. An example of both, when you want quickly want to hit a fly which landed on your arm without looking, the quick, almost unconscious movement of the arm towards the fly will be based on the body schema. If you want to take a close look at the fly and make a close estimation of the position of the fly on your arm, this process will be based on the body image.

Disorders of body representation can affect the entire body or only specific body parts. An example of a disorder in body image where only a specific body part is affected is finger agnosia. When experiencing this disorder, one is not able to identify the fingers, despite intact sensory and motor modalities. This occurs mostly in the middle three fingers of both hands (Frederiks, 1985, van Stralen, Zandvoort, Dijkerman 2011, Anema et al. 2008). In stroke patients, finger agnosia is the most common of all body representation disorders (Berkhof, 2013). Another body representation disorder concerns left-right disorientation. In this disorder the identification of the right and the left side of one's body is disturbed, while other spatial concepts (up-down, or front-back) and left-right identification of other objects and other persons remain intact (Denes, 1989, van Stralen, Zandvoort, Dijkerman 2011). Together with dyscalculia and dysgraphia, finger agnosia and left-right disorientation form Gerstmann's syndrome (Gerstmann 1942). However, a lack of uniformity in the prevalence of these 4 components makes this syndrome until today a controversial issue in neuropsychology (Lebrun, 2005, Rusconi, Pinel, Dehaene, Kleinschmidt, 2010).

Compared to disorders in other perceptual modalities, for example visual disorders, deficits in somatosensory modalities receive less attention both in research as well as in clinical

practice. As a consequence, the exact neurological substrate underlying body representation disorders remains unclear.

In contrast to deficits in the primary tactile detection, higher order deficits can occur bilaterally after a unilateral lesion. Several studies suggest a central role for the posterior parietal cortex, the secondary somatosensory cortex and the insula (Dijkerman, de Haan, 2007). In the present study we aim to provide insight in the neurological mechanisms underlying body representation disorders by linking neurological lesions with body representation disorders, i.e. finger agnosia, tactile localization impairments or left-right disorientation. Furthermore, the overlap and interplay between these impairments are mapped by using an advanced lesion-symptom mapping approach (Rorden and Karnath, 2004, Biesbroek et al., 2013). A major advantage of this method over traditional approaches to lesion mapping is that instead of grouping of patients with or without lesions in one or more predefined areas of interest, it allows for assumption-free calculation of association with the deficit at each voxel.
For measuring finger agnosia, the Finger Agnosia Task (FAT) by Anema et al. (2008) was used. To investigate the distinction between body image and body schema related to the presentation of the hand and fingers, we used the Tactile Pointing Task (TPT) based on the pointing task by Anema et al. (2009). In order to assess left-right discrimination, we used the first subtask ('back-condition') of the Bergen Left-Right Discrimination-task (BRLD-task) (Ofte, Hugdahl, 2002). To perform lesion-symptom mapping, the FAT, the BRLD-task and the TPT were administered in a cohort of patients with first-ever ischemic stroke. In addition, assumption-free voxel-based lesion-symptom mapping (VLSM) was performed, thus relating lesion location to performance on the FAT, the BRLD-task and the TPT. By comparing the anatomical correlates of impairments on these tests, we aim to isolate the neural components underlying finger recognition, left-right discrimination and the distinction between body image and body schema related to the hand. In this way we can determine the neural substrate of (this part) of body representation.

Based on former findings, it is expected the substrate of these aspects of body representation are located in the left posterior parietal cortex (Dijkerman, de Haan, 2007). Because finger agnosia and left-right disorientation are both symptoms of the Gerstmann's syndrome which is located primarily in the inferior posterior parietal areas of the dominant, mostly left hemisphere (Roux et al. 2003), it is expected that these symptoms are related to damage in these areas. Several neurophysiological studies suggest that particularly Brodmann area 5 (superior posterior parietal cortex) is involved in somatosensory processing concerning the body during goal directed arm movements (Colby, 1998, Gregoriou & Svaraki, 2001). Because of the pointing movement in the TPT, positive outcome on this task is expected to be linked to superior posterior parietal lesions (indicating the position on the hand, body schema) and the inferior parietal lesions (indicating the position on a drawing of the hand, body image)

(Dijkerman, de Haan, 2007). The current study is the first to apply these advanced lesion-symptom mapping methods to determine the anatomical substrates of body representation and to isolate the neuroanatomical substrates of left-right discrimination, finger agnosia and the distinction between body image and body schema of the hand.

METHODS

This master thesis displays the preliminary results of the lesion-overlap study aimed at body representation which is currently still in progress.

Participants:

17 Patients were included for this preliminary analysis. Data on all 17 patients was retrieved from a prospectively collected database of patients (database of the standard test battery of the Utrecht Stroke and COGnition study group (USCOG)) who were admitted at the University Medical Centre Utrecht (UMCU) after experiencing a stroke from July 2011 through September 2012 and met the following inclusion criteria: (1) Participants in the current study are adults (>18yrs), (2) first ever ischemic stroke, (3) an infarction on follow-up CT (≥ 2 days after stroke) or MRI (4) complete data on the FAT, BRLD,-task and the TPT.
In the current study the following exclusion criteria were used: (1) Participants with pre-existent neurologic conditions that might interfere with cognition (old infarcts on initial brain imaging, recurrent stroke between imaging and neuropsychological examination), (2) existence of a language barrier or diminished ability to speak due to severe global aphasia.

Tasks and Stimuli:

Concomitant with the standard test battery of the Utrecht Stroke and COGnition study group (USCOG), FAT, TPT and BRLD-task were administered. Administration of the USCOG test battery has a duration of 90 minutes. If the physical and mental health of the patient was not sufficient enough to undergo the full test-battery, testing took place in several shorter intervals during the day/several days.
Neuropsychological assessment was performed in the setting of standard clinical care. Background information and information about the administration, oral instruction and the used forms of FAT, TPT and BRLD-task are added in appendix 1, 2 and 3.
To make sure the outcome of the FAT, TPT and the BLRD-task was not influenced by deficits in the understanding of language or in primary somatosensory functioning, data of the Boston-naming test (to test confrontational word retrieval) and the single-touch items of the extinction-component of the FAT test (in this case to test deficits in detection of tactile stimuli on the hand) was used. If data of the Boston-naming test or the extinction component of the FAT was missing, the decision if the patient would be included was based on the clinical judgment and noted observations of the neuropsychologist.

Definition of norms of the FAT, BRLD-task and TPT :

Adequate age-related norms for the FAT, BRLD-task and TPT were not available. To create adequate age- related norms on the FAT was administered in a group of 30 healthy adult participants, selected on age and distribution of gender, matching the sample of patients, administered by two test leaders. The TPT and the BRLD-task were administered in a group of 25 healthy adults, based on the same selection, also by two test leaders. Exclusion criteria were the presence of neurological conditions that might interfere with cognition or the existence of a language barrier.

The Finger Agnosia Task

The 30 healthy controls measured in this study were administered by two test leaders (D.S, S.B.*). Although the outcome of the measurements on the FAT differed significant between the two test leaders (Mann-Whitney U z=-2.252, p=.024), we still chose to combine the measurements. The significant difference might have been due to the small number of measurements (11 vs 19) and because the test protocol left not much room for differences in administration of the task, the small sample size seems the only explanation for this significant difference. Possible effects of age and distribution of gender between the control- and patient group were examined. A Mann-Whitney U test showed no significant differences in distribution of gender (z=-1.343, p= .179) between the control- and patient group. An independent samples t-test showed no significant difference in age between the control- and patient group ($t\ (45) = -.99, p= .922$). The norm data of the FAT was not normally distributed (Kolmogorov-Smirnov p<.000), resulting in the calculation of a median and interquartile range (IQR). The median and IQR of the number correct items are displayed in table 1. Because 3.3% (less than 2 SD) of the control group has a score of 10/14, the cut-off for a positive score on finger agnosia used in this study is 10/14 correct items or less. To make sure a positive score were not due to deficits in word retrieval and/or primary tactile functioning; patients must not had positive scores on the Boston naming task and/or the single items of the extinction task. Patients could serve as controls when they had 14/14 items correct.

**D.S.= D. Sluiter, S.B. = S. Bos*

The Tactile Pointing Task

The 25 healthy controls measured in this study were administered by two test leaders (D.S, S.B.*). Although the outcome of the TPT – directing to the drawing of the hand differed significant between the test leaders (Independent samples t - test: t (23)= -4.913, p <.05), we still chose to combine the measurements. The significant difference might have been due to the small number of measurements (14 vs 11), and because the test protocol left not much room for

differences in administration of the task, the small sample size seems the only explanation for this significant difference.

Possible effects of age and distribution of gender between the control- and patient group were examined. A Mann-Whitney U test showed no significant differences in distribution of gender (z=-1.098, p= .272) between the control- and patient group. An independent samples t-test showed no significant difference in age between the control- and patient group (*t (40) = .153, p= .879*).. The mean and the SD of the distance between the touch on the hand and the indication of the position on the own hand or the schematic drawing of the hand are displayed in table 1. The mean distance was calculated over 3 trials. The cut off is at 3 SD above the mean, rounded to whole cm, which is 4 cm. If a patient had a larger distance than 4 cm at two of the 3 trials per hand, (at one or both hands), performance was considered to be disturbed. To make sure this was not due to deficits in primary tactile functioning, patients must not had a positive score on the single tactile detection of the extinction task.

Because this task contains the pointing movement as a motoric component, it is important that the outcome of this task is not influenced by impaired motor skills or proprioception of the arm as a consequence of the infarction. None of the patients showed impairments in both directing to the hand and directing to the schematic drawing of the hand, which means that the basic motoric skills required to make the directing- movement were not influenced by impairments in motor skills or proprioception of the contralesional arm. Because of this, the author considers deficits on this task in this sample of patients reflecting a deficit in body image or body schema. No distinction is made between directing with the ipsi- or contralesional arm in the analyses of this task.

Patients could serve as controls when they had at 2 of the 3 trials per hand a smaller distance than 2 cm, and none of the distances larger than 4 cm.

**D.S.= D. Sluiter, S.B. = S. Bos*

The Bergen Left-Right Discrimination-task

The 25 healthy controls measured in this study were administered by two test leaders (D.S, S.G.*). Although the outcome of the measurements differed significantly between the test leaders (Mann-Whitney U z=-2.301, p=.021), we still chose to combine the measurements. The significant difference might have been due to the small number of measurements (6 vs 19), and because the test protocol left not much room for differences in administration of the task, the small sample size seems the only explanation for this significant difference. Possible effects of age and distribution of gender between the control- and patient group were examined. A Mann-Whitney U test showed no significant differences in distribution of gender (z=-1.343, p= .179) between the control- and patient group. An independent samples t-test showed no significant

difference in age between the control- and patient group (*t (40) = .977, p= .334*)..The mean and the SD of the percentage of good items of the back-condition are displayed in table 1. The cut-off is set at 3 SD below the mean (71.35%) rounded to 70% correct items or less. To make sure a positive score could not be due to deficits in word retrieval, patients must not have had positive score on the Boston naming task. Patients could serve as controls when they had 90% of the items correct, and finished at least 10 items.

**D.S.= D. Sluiter, S.B. = S. Gerdingh*

Table 1. Sample sizes, means, medians, standard deviations and inter quartile ranges per task of the norm group.

Task	N	M(*)	SD / [IQR]
FAT	30	14*	[14-13]
TPT – own hand	25	1.5	.67
TPT – drawing of hand	25	1.57	.8
BRLD- task	25	96.22	8.29

N=sample size, M=mean, M=median, SD=standard deviation, [IQR]= inter quartile range*

Generation of lesion maps:

Infarctions were manually delineated in either CT (n=9) or MRI (n=8). Segmentation in the current study was performed by two trained reviewers (initial segmentation by D.S.* and H.v.S,* followed by a review by J.M.B.* (followed by a consensus review if necessary)). The scans used for this preliminary analysis are segmented only by J.M.B. Reviewers were blinded to neuropsychological data to prevent potential bias. Only CT scans that were performed > 48 hours after the onset were used, this criterion was not used for MRI scans because diffusion-weighted imaging allows for detection of the ischemic lesion within hours from symptom onset. All scans were performed in the setting of standard clinical care. For the CT scans, a Philips Mx8000 16, Brilliance 64, or Brilliance 256 CT scanner was used. MRI scans were made using either a Philips Interna (1.5 Tesla) or Philips Achieva (1.5 or 3.0 Tesla) scanner. The lesion maps were subsequently registered to the T1-MNI-152 (Montreal Neurological Institute). For registration to standard space, a lesion-masking approach was applied to enhance registration quality; lesion masks were created by subtracting infarct lesion maps from brain masks. After registration of the T2 FLAIR, warp fields were used to co-register the corresponding infarct maps to the 1-mm MNI template. The same registration method was applied to the CT-scans using a registration algorithm that was designed and validated for this purpose (Kuijf et al., 2013). Quality checks of the registration were performed by comparing the native scan to the

lesion in MNI space. Manually adjustments to correct slight registration errors were performed by J.M.B. using MRIcron (http://www.mccauslandcenter.sc.edu/mricro/mricron).
**D.S. = D. Sluiter, H.v.S.= H. v. Stralen, J.M.B= J.M. Biesbroek*

Statistics :

Voxel-based lesion mapping was used to determine the relationship between behavioral measures and the location of ischemic lesions (Rorden and Karnath, 2004, Biesbroek et al, 2013). We performed VLSM using a dichotomized performance on the FAT, TPT and BRLD-task, based on the predefined norms and cut-offs per task (deficit: yes/no, control: yes/no). Correction for multiple testing was achieved using a false detection rate (FDR) with $q<0.05$. These results were projected on the MNI template.
If the VLSM analysis gained no significant results, a qualitative lesion subtraction analysis was performed.

RESULTS

Clinical characteristics of the study cohort are provided in table 2.
Per task the outcome of the VLSM analysis and the spatial distribution of infarcts illustrated by the lesion prevalence maps will be displayed.

Characteristics	Study cohort (n=17)	
Demographic characteristics		
Age in years (mean, SD)	57.8 (14.4)	
Male, n (%)	13 (76.5%)	
Handedness Right n (%)	16 (94.1%)	
Time between stroke and NPE in days (mean, SD)	5.6 (4.6)	
Body representation tasks	*Impaired, n (%)*	*Control, n (%)*
Finger Agnosia Task	3 (17.6%)	10 (58.8%)
Tactile Pointing Task:		
Indicating to hand	2 (11.8%)	9 (52.9%)
Indicating on Schematic drawing	2 (11.8%)	9 (52.9%)
Bergen Left-Right Discrimination-task	3 (17.6%)	7 (41.2%)

Table 2. Characteristics of the study cohort and outcome neuropsychological examination

Finger Agnosia Task

Voxel-based lesion-symptom mapping with dichotomized cognitive performance of the FAT as outcome (impaired yes/no) showed no significant outcome, using the Liebermeister test FDR q<.05. The range of Z-scores in this analysis was L Range was -.701 – 2.374. For significant results voxels needed to exceed the FDR threshold of 9.20 (False Discovery Rate Correction L - FDR Z .05 = 9.20) to be significant. To gain insight in the location of the lesions related to positive scores on the FAT, a qualitative lesion subtraction analysis was performed. Results are

displayed in figure 1. Lesions related to deficits in finger gnosis are mainly located in the right hemisphere, more specifically the caudate nucleus, external capsule, putamen and frontal cortex.

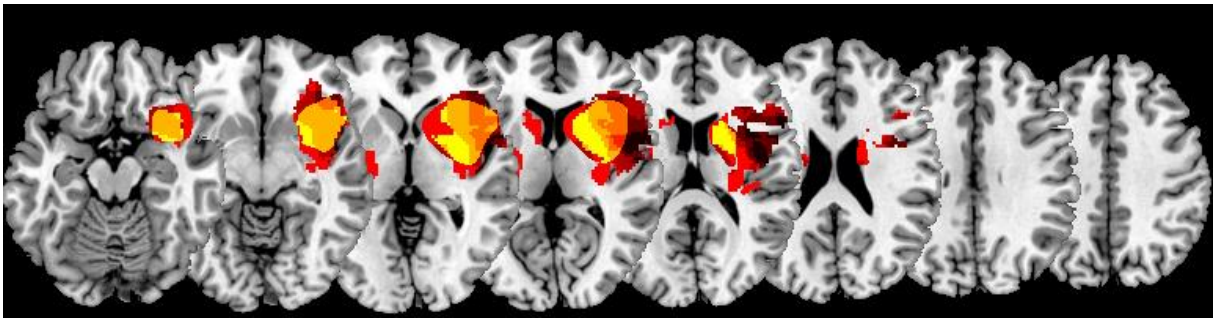

Fig. 1. Outcome of qualitative lesion subtraction analysis of the location of lesions related to positive scores on the FAT. Left side in the figure corresponds with the left side of the brain. Red, and yellow colored areas are the lesion areas associated with deficits on the FAT. Please note that the presented subtraction represents a descriptive difference; no interferential statistical testing was performed here.

Tactile Pointing Task, indicating the position on the hand

Voxel-based lesion-symptom mapping with dichotomized cognitive performance of the TPT – indicating on the hand as outcome (impaired yes/no) showed no significant outcome, using the Liebermeister test FDR q<.05. The range of Z-scores in this analysis was L Range was -.203 – 1.769. For significant results voxels needed to exceed the FDR threshold of 9.20 (False Discovery Rate Correction L - FDR Z .05 = 9.20), so results were not significant. To gain insight in the location of the lesions related to positive scores on the TPT – indicating on the hand, a qualitative lesion subtraction analysis was performed. Results are displayed in figure 2. Lesions related to deficits on body schema are mainly located in the right hemisphere, more specifically the nucleus caudatus, capsula externa and putamen.

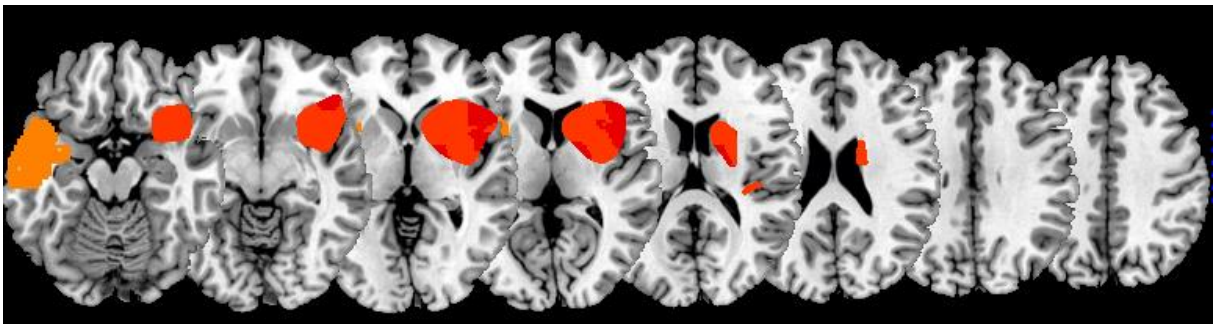

Fig. 2. Outcome of qualitative lesion subtraction analysis of the location of lesions related to positive scores on the TPT – indicating the position on the hand. Left side in the figure corresponds with the left side of the brain. Red, and yellow colored areas are the lesion areas associated with deficits on the TPT – indicating the position on the hand. Please note that the presented subtraction represents a descriptive difference; no interferential statistical testing was performed here.

Tactile Pointing Task, indicating the position on the schematic drawing of the hand

Voxel-based lesion-symptom mapping with dichotomized cognitive performance of the TPT – indicating the position on the schematic drawing of the hand as outcome (impaired yes/no) showed no significant outcome, using the Liebermeister test FDR q<.05. The range of Z-scores in this analysis was L Range was -.203 – 1.769. For significant results voxels needed to exceed the FDR threshold of 9.20 (False Discovery Rate Correction L - FDR Z .05 = 9.20), so results were not significant. To gain insight in the location of the lesions related to positive scores on the TPT – indicating the position on the schematic drawing of the hand, a qualitative lesion subtraction analysis was performed. Results are displayed in figure 3. Lesions related to deficits in body image are mainly located in the right hemisphere, more specifically the nucleus caudatus, capsula externa, and putamen.

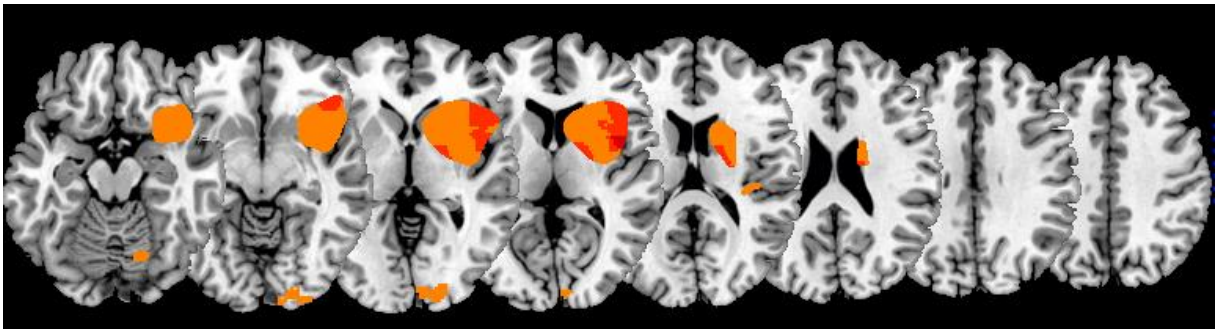

Fig.3. Outcome of qualitative lesion subtraction analysis of the location of lesions related to positive scores on the TPT – indicating the position on the schematic drawing of the hand. Left side in the figure corresponds with the left side of the brain. Red, and yellow colored areas are the lesion areas

associated with deficits on the TPT – indicating the position on the schematic drawing of the hand. Please note that the presented subtraction represents a descriptive difference; no interferential statistical testing was performed here.

The Bergen Left-Right Discrimination-task

Voxel-based lesion-symptom mapping with dichotomized cognitive performance of the BRLD-task as outcome (impaired yes/no) showed significant outcome, using the Liebermeister test FDR q<.05. The range of Z-scores in this analysis was L Range was -0.660 - 2.875. For significant results voxels needed to exceed the FDR threshold of 2.09 (False Discovery Rate Correction L - FDR Z .05 = 2.09), so voxels above this threshold were significant. The location of the significant voxels is displayed in figure 4. Lesions related to deficits in left right orientation are mainly located in the right hemisphere, more specifically the nucleus caudatus, capsula externa and putamen.

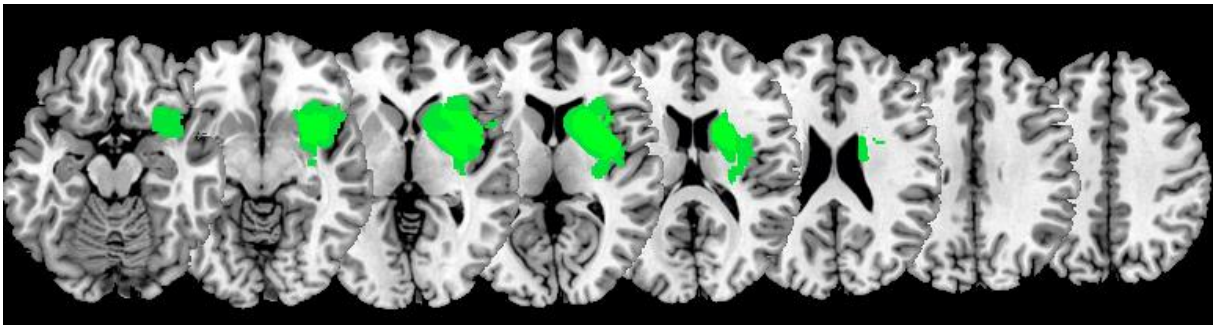

Fig. 4. Voxel based lesion mapping with dichotomized performance on the BRLD-task as outcome. Voxels that are damaged significantly (q<.05) *more often in patients with the deficit are shown in green. Left side in the figure corresponds with the left side of the brain.*

Overall substraction – all tasks combined

To gain insight in the location of the lesions related to the concept body representation a qualitative lesion subtraction analysis was performed to display the location of the lesions related to one or more positive outcome on the tasks. Results are displayed in figure 5. Lesions related to deficits in body representation are mainly located in the right hemisphere, more specifically the nucleus caudatus, capsula externa, putamen and frontal cortex.

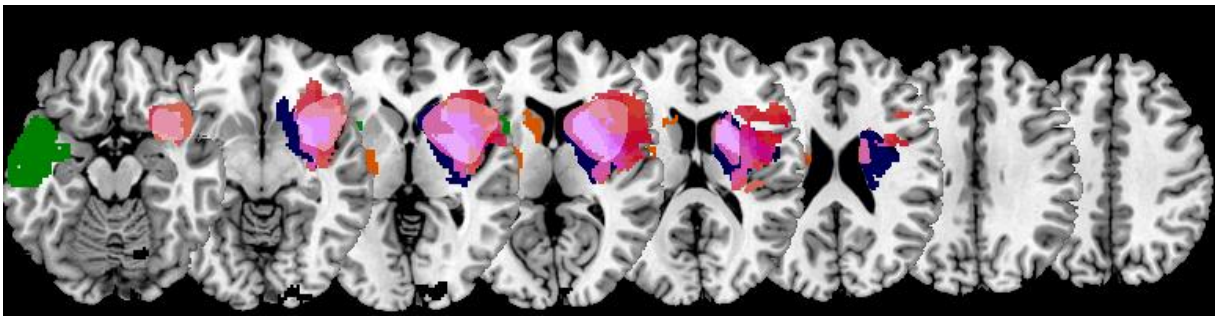

Fig. 5. Outcome of qualitative lesion subtraction analysis of the location of lesions related to positive scores on one or more of the four tasks. Left side in the figure corresponds with the left side of the brain. Colored areas are the lesion areas associated with deficits on the body representation tasks. Please note that the presented subtraction represents a descriptive difference; no interferential statistical testing was performed here.

DISCUSSION

In the preliminary analyses of the present study we used lesion-symptom mapping in first episode-stroke patients to determine the anatomical correlates of body representation. Three known body representation disorders were investigated, i.e. finger agnosia, tactile mislocalisation and left right disorientation. The voxel-based lesion-symptom mapping analysis of the anatomical correlate related to left right orientation gained significant results: lesions related to left right disorientation are mainly located in the right hemisphere, more specifically the caudate nucleus, external capsule and putamen. Although lesion mapping analyses on the finger agnosia and tactile mislocalisation gained no significant results, a qualitative lesion subtraction analysis shows a trend that lesions related to these tasks are also mainly situated in the right hemisphere, more specifically the caudate nucleus, external capsule, putamen and frontal cortex. These preliminary results indicate that parts of the basal ganglia and the external capsule of the right hemisphere are key anatomical structures in these components of body representation.

These findings are not in line with our expectations based on previous findings which indicate body representation would be situated in the posterior parietal cortex (Dijkerman, de Haan, 2007, Roux et al. 2003). Although several studies indicate that components of body representation as signs of the Gerstmann's syndrome might be located not only in the posterior parietal cortex, but also on other locations in the dominant-, and even in the non-dominant hemisphere (Strub, Geschwind, 1983, Lebrun, 2005), the trend shown in the preliminary results of the current study are at least remarkable. A possible explanation lies in the theory that deficits in body representation might be related to the same anatomical structures as deficits in spatial awareness. Karnath et al. (2004) showed in a lesion-overlap study that lesions to the right superior temporal cortex, the insula, subcortically putamen and caudate nucleus are typically associated with spatial neglect in humans. This could indicate that body representation is not an isolated function with an isolated location in the brain, but that it is closely related, even intertwined with spatial awareness. However, Vallar and colleagues (1997) showed in a study using different rehabilitation techniques a clear dissociation between position sense of the arm (based on body representation) and the visual-spatial components of neglect (based on spatial awareness). Although neglect and position sense disorders of the arm are frequently associated, this indicates that body representation and spatial are dissociated. Deficits in spatial awareness do not account fully for deficits in body representation and vice versa.

Body representation is closely related to body ownership. Where body representation can be seen as a more structural representation of our body parts and total body, body ownership is a fundamental aspect of self-consciousness regarding the body. It can be described as a feeling of ownership of our limbs and total body. Zeller and colleagues (2011) performed a

study to investigate the role of the ventral premotor cortex in changes in body ownership. To investigate this, they used the Rubber Hand Illusion. In this illusion subjects develop feelings of body ownership of a rubber hand placed in front of them if the viewed rubber hand and the subject's covered own hand are repeatedly stroked simultaneously (Botvinick and Cohen, 1998). According to an earlier functional imaging study, the feelings of body ownership during the rubber hand illusion are associated with activity in the ventral premotor cortex (Ehrson et al 2005 etc). The ventral premotor cortex is believed to play a key role in the integration of multisensory inputs, essential to allow the incorporation of the rubber hand into the body representation. It seems an essential structure in this process, because of its anatomical connections with visual and somatosensory areas in the posterior parietal cortex and motor areas (Rizzolatti et al, 1998). To obtain a causal structure function relationship, Zeller and colleagues (2011) used a voxel based lesion symptom mapping approach, investigating the essential voxels of lesions in patients who display deficits in the development of feelings of body ownership during the rubber hand illusion. Probabilistic diffusion tractography was used to identify tracts passing through these voxels. Results were that voxels associated to deficits in the development of feelings of body ownership during the rubber hand illusion were located subcortically adjacent to the insula, basal ganglia and within the periventricular white matter. Tractography revealed fiber tract connections of these voxels with premotor, parietal and prefrontal cortex. These results indicate that the insula, basal ganglia and periventricular white matter are key structures in a larger network regarding body ownership and body representation, including the premotor, parietal and prefrontal cortices.

The results in this master thesis show similarities with the results from Zeller and colleagues (2011). Voxels related to deficits in body representation were also located subcortically adjacent to the basal ganglia and periventricular white matter. Body ownership and body representation are closely related. It is possible that lesions in the structures in this thesis are part of a similar network displayed in the study of Zeller at al. (2011). That would mean that not solely the basal ganglia and parts prefrontal cortex displayed in the current analysis are essential in body representation, but that they are key structures in a bigger network, possibly also including parietal and frontal cortices. In future studies, voxel based lesion symptom mapping analyses in combination with analyses using tractography could reveal not only the essential key structures in body representation, but also the complete neural network which these structures are part of.

In this thesis results show that left right disorientation is significantly related to damage to the caudate nucleus, external capsule and putamen. To reason what is left and right the position of our body parts and total body in relation to each other and our surrounding space is used as a structural frame of reference. Because of this, these brain areas seem related to a more

structural representation of the body. In the study of Zeller at al. (2011) results show that the basal ganglia and insula are related to body ownership. The connection between the basal ganglia, related to a more structural representation of the body, and the insula seems essential in body ownership. Hypothesizing this could mean that the insula is a key structure in self-consciousness of the body, which in combination with the basal ganglia forms a key connection responsible for feelings of in body ownership.

In another study, Schwoebel and Branch Coslett (2005) used a lesion symptom mapping approach to investigate the neural substrate of different forms of body representation. Their results showed that dorsolateral frontal regions and parietal regions are associated with deficits on tasks requiring on-line coding of body posture (body schema), whereas the left temporal lobe was consistently associated with deficits on tasks assessing knowledge of the shape or lexical-semantic information about the body (body image). Results of Schwoebel and Branch Coslett (2005) show that when investigating the networks associated with body representation in future studies, we should broaden our vision regarding which brain regions will be involved.

A limitation of these preliminary VLSM analyses is that the sample used is relatively small. Due to limited time concerning the completion of the inclusion of patients and scans, it was not possible to use the complete data for this thesis. Because of this, we chose a very robust analysis, namely that we dichotomized our data in the presence of an impairment on the tasks, or not. This robust analysis does not account for the severity of the deficit. When performing the main analysis when all the data is available, it might be more elegant to use the patient data as on the three tasks as a continuous variable as well to see if smaller differences in performance on the tasks will correspond with selective anatomic correlates. Although a trend is shown in location of the lesions related to body representation in the current analysis, the results of this thesis should be interpreted with care. They only give directions to what the possible outcome of the main analyses might be, which will contain a bigger sample with between forty and fifty patients.

Another limitation to the current analysis is that we only segmented and analyzed damaged brain tissue due to the infarction. Factors as the atrophy of the brain or the influence of small white matter lesions or small lacunar infarctions were not segmented, and in this way not accounted for in this analysis. A recent study using VLSM shows a significant correlation between white matter lesions and executive functioning (Biesbroek et al., 2013). Because of this, the presence of small white matter lesions might have interfered with the outcome on the neuropsychological tests, even though they are not segmented and accounted for in the lesion-symptom analysis and so possibly could have blurred the results. Although the presence of non-segmented, small white matter lesions or lacunar infarctions might have had an influence on executive functions in cognitive functioning in the current study, the trend shown that lesions in

these analyses are situated in the right hemisphere is still very clear. Nevertheless, adjustment for white matter lesions, small lacunar infarctions and brain atrophy is recommended for the main analysis on the complete set of data to get as valid results as possible.

In summary, the current preliminary analyses demonstrate right hemispherical correlates related to left-right orientation and more specifically in parts of the basal ganglia and the external capsule. Qualitative lesion subtraction analyses show a trend that lesions related to finger agnosia or deficits in body image and/or body schema are also mainly situated in the right hemisphere, more specifically the caudate nucleus, external capsule, putamen and frontal cortex. A possible explanation is that these structures are not solely responsible for these components of body representation, but that they are key structures in a bigger network, possibly also including parietal and frontal cortices. Future studies combining a voxel based lesion symptom mapping approach in combination with probabilistic diffusion tractography are recommended. A combination of these two methods could provide insight not only in the key structures essential for body representation, but also the neural networks which these structures are an essential part of.

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APPENDIX 1

Background information and administration

The Finger Agnosia Task tests the representation and identification of the fingers. The task is based on the FAT used by Anema et al. (2008). The participant should be blindfolded, sitting with both arms stretched on the table (palms down). First the participant is asked to name all of his/her fingers. Next step is that the researcher shortly touches (1 sec.) the fingers in the order described on the test form, participant has to say which finger was touched. If the participant is experiencing difficulties naming the finger, he/she is asked to point the touched finger of a plasticized card with a drawing of a hand on it (dorsal view). In total 14 trials are performed. Time: 5 minutes.

The Bergen Left-Right Discrimination Task (Ofte, Hugdahl, 2002) will be administered to measure the capability of the participant to distinguish left from right. The task consists of line figures of a man with none, one or two arms crossed over the body-axis of the figure. Goal of the task is to mark as fast as possible the initiated left or right hand of the figure. The task contains three conditions, one where you see the man positioned from the back, one positioned from the front, and one both in random order. The goal of the stimuli positioned from the back is to measure left-right discrimination, the goal of the stimuli from the front is to measure the ability to make a mental rotation of the figure, the goal of both stimuli in random order measures the ability to shift between these two concepts. In the current study, the back-condition is used as a measure for left-right discrimination. For each condition the participant has 90 sec to finish as many items as possible. Time: 5-8 minutes.

The Tactile Pointing Task is based on research performed by Anema et al. 2009 and measures possible disorders in body schema or body image (Paillard, 1999, Gallagher, 2005). Anema et al. (2008) described in 3 case studies of patients suspected of having finger agnosia that all three patients exhibited impaired performance in a task that was hypothesized to activate body image, by naming a touched finger or pointing towards it on a schematic drawing of the hand. In contrast, the three patients performed normally when asked to point directly to the touched finger without the aid of visual or semantic feedback, which is considered to involve the body schema. Using a similar pointing task, Anema et al. reported in 2009 a unique double dissociation between body schema and body image in two stroke patients with intact basic somatosensory processing.

In the first condition, the participant will be sitting blindfolded with the arms resting on a table,

palms down. The researcher makes a small dot with a pen on a random place on the hand of forearm of the patient (contra- and ipsilesional). The participant is asked two point as accurately with the other hand to the place where the researcher put the dot. Using a ruler, the researcher measures the distance between the dot and the location pointed by the participant. Three trials each hand.

In the second condition the participant will be sitting blindfolded in the same position as in the first condition. Again, the researcher makes a small dot with a pen on a random place on the hand of forearm of the patient (contra- and ipsilesional). After this the participant is asked to put the hand on his/her lap, out of sight, and to point out the location of the dot with the other hand on a schematic drawing of the hand. Using a ruler, the researcher measures the distance between the dot and the location pointed by the participant. Three trials each hand. Time: 5-8 minutes.

APPENDIX 2

Oral instructions

The Finger Agnosia Task

"In a moment I will shortly touch one of your ten fingers. I would like you to tell me which finger I have touched."

The Bergen Left-Right Discrimination Task

""In a moment I will show you several line figures of a person, positioned from the front and from the back. The shoulders of the person are pictured with a black triangle. The hands contain of two circles. Under each line figure there is a letter: R for the right hand and L for the left hand. You are ought to mark the circle with an X of the right hand if there is an R under the figure, and the left hand if there is an L. make sure you will mark the circles with an X.

Here is an example (show example-figure on test form)

Do this for all the figures in the test. The test contains three stages en each stage contains three pages. Work as fast and accurate as possible. The time you have is limited. Stop when you have finished the pages or when I will tell you to stop."

The Tactile Pointing Task

Instruction pointing to own hand: *" I will make a small dot with a pen on a random place on your hand or forearm. After this I will ask you if you could point with your other hand as accurately as possible where I put the dot. You are allowed to point to this place, and keep your finger on this place for a short moment, so I can measure where you put your finger. Don't try to move with your finger once you'll have touched your hand/forearm."*

Instruction pointing to schematic hand: *" Again, I will make a small dot with a pen on a random place on your hand or forearm. After this I will ask you if you could place the hand with the dot on your lap, where you cannot see it. After this, could you point out on this schematic drawing of the hand the location which is as most in accordance as possible with the dot on your hand? "*

APPENDIX 3

Test form Finger Agnosia Task

Vingeragnosie + extinctie

Benodigdheden:
- schematische tekening van L en R hand
- houten box waarin handen niet zichtbaar zijn voor de participant.

Setting:
Participant zit (bij zowel deel 1 als 2) geblinddoekt met beide armen vooruit, handpalmen naar beneden. De taak bestaat uit 2 delen. Laat de participant voor de start eerst alle vingers benoemen.

1. Agnosie

Instructie:
"Ik ga kort één van uw tien vingers kort aanraken. Ik wil u vragen om daarna te benoemen welke vinger ik heb aangeraakt. Ik wil graag dat u uw vingers stilhoudt."
Methode:
Raak één vinger kort aan met de dikste Von Frey Hair en laat de participant de naam van de vinger opnoemen. Bij problemen met benoemen, laat de afbeelding van de hand zien en vraag de participant aan te wijzen welke vinger is aangeraakt.

2. Extinctie

Instructie:
"Ik ga nu soms één vinger, maar soms ook twee vingers tegelijkertijd aanraken. Ik zou daarna van u willen weten welke vingers ik heb aangeraakt. Als u dat niet weet, mag u ook zeggen of ik er 1 of 2 heb aangeraakt.
Methode:
Raak volgens instructie één vinger of twee vingers (simultaan) aan, degene beschreven volgens de tabel hieronder.

Agnosie		Benoem √ / X	Afbeelding √ / X	**Extinctie (raak ik 1 of 2 vingers aan?)**		**1 of 2?**	Indien fout, welke hand?
1.	re. ring			1	re. wijs + li. ring		
2.	re. middel			2	re. middel		
3.	re. wijs			3	re. ring + li. middel		
4.	re. duim			4.	re. pink + li. wijs		
5.	re. middel			5.	li. middel		
6.	re. pink			6.	re. duim		
7.	re. ring			7.	re. ring + li. middel		
8.	li. pink			8.	li. pink		
9.	li. duim			9.	re. duim + li. ring		
10.	li. wijs			10.	re. wijs + li. middel		
11.	li. middel			11.	li. ring		
12.	li. wijs			12.	re. middel + li. middel		
13.	li. ring			13.	re. ring + li. wijs		
14.	li. middel			14.	re. duim + li. duim		
Totaal aantal fout:				**Totaal aantal fout:**			

Test form Tactile pointing task / schematic drawing of the hand

Tactiel Wijzen

De taak bestaat uit 2 delen.

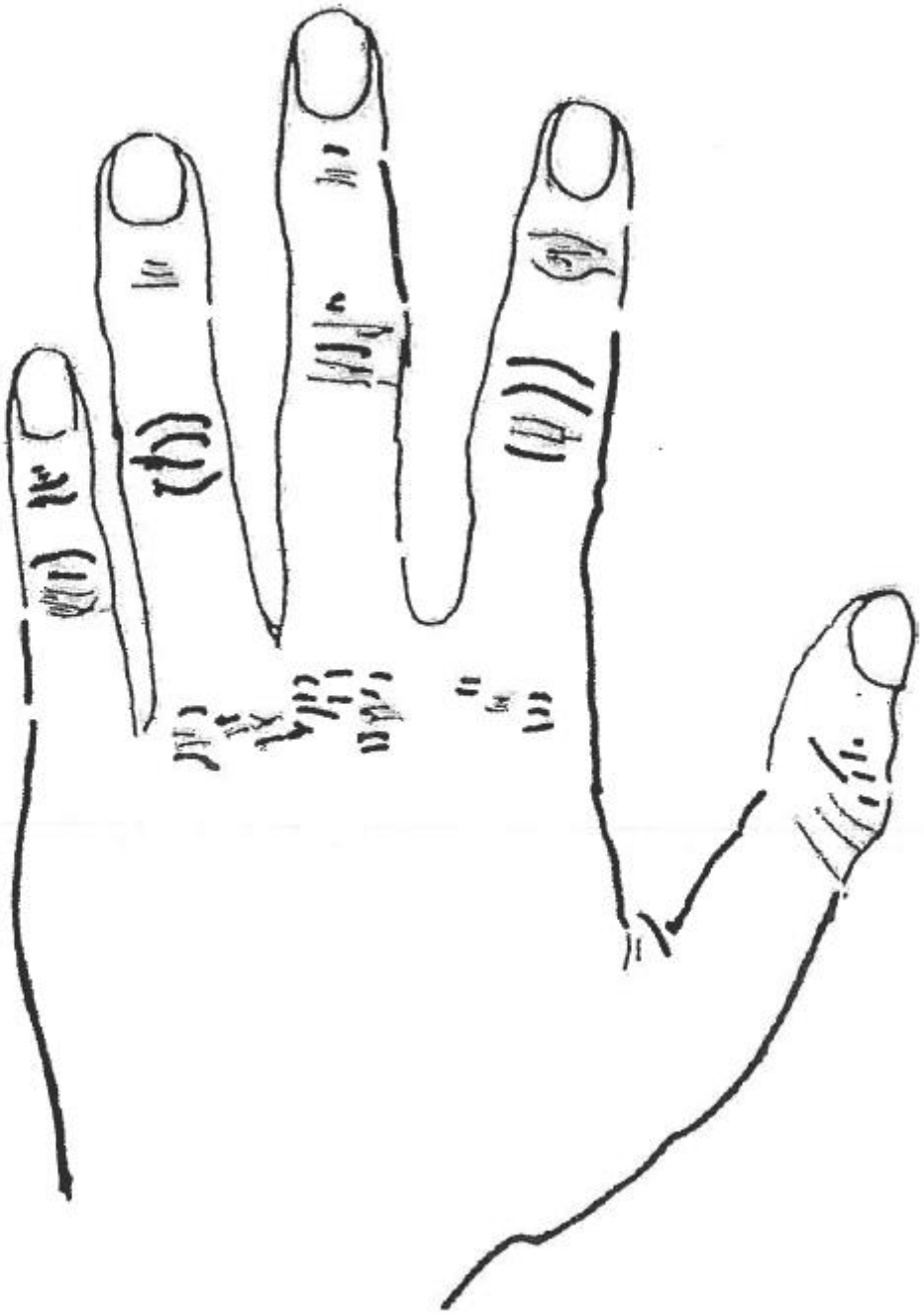
1. **Wijzen naar eigen hand**

Setting:
Participant zit geblinddoekt met beide armen vooruit, handpalmen naar beneden.
Instructie:
"Ik ga straks ergens met een pen een stipje ergens op uw hand of onderarm zetten. Dan ga ik u vragen of u met uw andere hand zo precies mogelijk aan wilt geven waar ik dat stipje heb neergezet. U mag wijzen en uw vinger op die plek even vasthouden zodat ik op kan meten waar u deze heeft neergezet. Probeert u niet meer uw vinger te schuiven zodra u uw hand of onderarm aanraakt"
Methode:
Zet met een pen een stipje in beneden het midden van de handpalm. Normale druk uitoefenen, maar niet te hard. Na het wijzen meet je met een liniaal op hoeveel cm. de participant naast het stipje wijst (na het eerste contact die de hand met de vinger heeft).

2. **Wijzen naar schematische hand**

Instructie:
"Wilt u nu uw hand waar ik net de stip op heb gezet op uw schoot leggen?" [nb. Deze mag niet zichtbaar zijn voor de participant!]. "Wilt u dan op dit formulier [schematische hand, links of rechts, afhankelijk waar net de stip op is gezet] een stip op de schematische hand zetten in overeenstemming met de locatie van de stip op uw hand."
Methode:
Geef papier en laat de participant met een pen een stip tekenen. Zorg dat hij/zij niet in staat is te kijken op zijn/haar eigen hand waar de stip staat.
Vul in onderstaand schema de bevindingen in.

Target-hand	Lokatie stip	Afwijking (cm) Wijzen Eigen Hand	Afwijking (cm) Wijzen Afbeelding
Linkerhand	hand 1	..... cm.	..... cm.
	hand 2	..... cm.	..... cm.
	hand 3	..... cm.	..... cm.
Rechterhand	hand 1	..... cm.	..... cm.
	hand 2	..... cm.	..... cm.
	hand 3	..... cm.	..... cm.



Example sheet Bergen Left-Right Discrimination-task Back condition