Universiteit Utrecht

Additional outcome measures and neural correlates of visuospatial construction using the Rey-Osterrieth complex figure and voxel-based lesion-symptom mapping

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Abstract

We studied visuospatial construction as measured by the Rey-Osterrieth Complex Figure test (ROCF) in detail, using more specified variables: (1) Figure Size; (2) Side of omissions; (3) Local vs. global items; and (4) Figure location. The correlation between these variables and five other, related neuropsychological tests was also examined. Last, voxel-based lesion-symptom mapping (VLSM) was performed to find neural correlates of said variables. The study cohort was a relatively large sample of first-ever ischemic stroke patients with an infarction on follow-up CT or MRI. Figure size was larger (μ=1.07), left side items were drawn correctly more often than right side items (0.81 vs. 0.69), local items were drawn correctly less often than global items (0.75 vs. 0.79) and the figure was located to the left (μ=-7.15). . Number of drawn left side, right side, local, and global items showed comparable correlations with the other neuropsychological tests. The right insula and right caudate nucleus were associated with left side and local items. The right angular gyrus and the occipital cortex were associated with right side and global items. The putamen was associated with global items. . Taken together, the results suggest that visuospatial construction is not a singular ability, but rather many collaborating components which can be selectively impaired.

Keywords: Visuospatial construction, Rey-Osterrieth complex figure, voxel-based lesion-symptom mapping, stroke

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Introduction

Visuospatial construction consists of the ability to see an object or picture as a set of parts and then construct a replica of the original from these parts (Mervis, Robinson, & Pani, 1999). In daily life, visuospatial construction is of major importance, e.g. when you get dressed, draw a picture or build a desk from unassembled parts. Despite individual differences in performing these activities (e.g., a construction worker will probably build a better desk than a lawyer), the underlying construct – visuospatial construction – comes naturally for most people. However, when you suffer a stroke for example, visuospatial construction can become impaired, and as all the associated functions can be affected, this impairment can be of a severe nature. Visuospatial construction relies on visuospatial perception, but is also associated with executive functioning and attention in general (Ashton, Donders, & Hoffman, 2005). A neuropsychological way of measuring visual construction is through implementation of the Rey-Osterrieth Complex Figure.

The Rey-Osterrieth Complex Figure Test was originally designed to assess visuospatial, constructive and executive abilities and visual memory (A. Poreh & S. Shye, 1998). The traditional test battery, standardized and normed by Osterrieth, one of Rey's students, consists of 18 elements. The complete test consists of a direct copy (with the original Rey Figure in front of the subject), an immediate recall (3 minutes after administration, without the original Rey Figure), a delayed recall (30 minutes after administration) and a recognition trial in which the patient has to decide whether or not shown elements were present in the Rey Figure. Lower scores on the ROCF point toward lower visuospatial, constructive and/or executive abilities or impaired visual memory. For the remainder of this paper, this score will be referred to as the original ROCF score as measured by Osterrieth.

With respect to figure size (1), a study by Loughan, Perna, & Galbreath (2012) suggested a relation between figure size and general score on the ROCF. It is imaginable that drawing a large figure would allow easier replication of details compared to drawing a small figure and thus influencing the general score. Moreover, since the subject is asked to replicate the figure as accurately as possible, an unrepresentative figure size reflects either poor understanding of the assignment or diminished visuoconstructive ability.

As for side of omissions (2), another study (Biesbroek et al., 2014) suggested the possibility of distinct lesion locations causing specific error types. One such error type could be the omission in drawing one or more left sided items versus the omission of drawing one or more right sided items, as suggested by Karnath, Fruhmann Berger, Kuker, and Rorden (2004). Due to prior research we thought this variable would be interesting to study, despite neglect being one of our exclusion criteria (see method section. That is, we expected more subtle differences in performance can still be found in non-neglect patients.

Another comparison we could make based on this logic would be the distinction between drawing local items versus drawing global items (3), as suggested by other authors (A. Poreh & S. Shye, 1998; Stiles et al., 2008). In the study conducted by Stiles and colleagues, right hemisphere brain lesions where correlated with impaired performance on processing global items. Left hemisphere brain lesions on the other hand, correlated with impaired performance on processing local items.

Finally, the location of the replicated figure (4) might be affected by, for example, neglect or visuospatial deficiencies, which has been discussed in several studies (Stiles et al., 2008; Trojano et al., 2004). Since very little research has been conducted on the ROCF combined with the location of the copied figure, this would be an interesting feature to study.

Ideally, a test is standardized in order to measure as much information possible regarding the variable that is being tested. Especially in clinical settings, where the focus is assessment of the individual's cognitive functioning, specified information about a subject's functioning is essential to the quality of the treatment that can be offered. The more specific the information a test acquires, the better we are able to map visuospatial construction. With regard to this, there are many more novel measures we can extract from the ROCF besides just direct or delayed reconstruction of the figure. The primary aim of this study was to assess visuospatial and visuoconstructive processing as measured with the ROCF in more detail, in a relatively large sample of stroke patients. The additional outcome measures for detailed assessment of visuospatial and visuoconstructive processing are: (1) figure size (larger versus smaller compared to original) (Loughan, Perna, & Galbreath, 2014); (2) side of omissions (left versus right)(Luukkainen-Markkula, Tarkka, Pitkänen, Sivenius, & Hämäläinen, 2011; Rapport, Farchione, Dutra, Webster, & Charter, 1996); (3) local versus global items (Amir Poreh & Samuel Shye, 1998)); and (4) figure location (both horizontal and vertical location)(Lange, Waked, Kirshblum, & DeLuca, 2000; Trojano et al., 2004).

The secondary aim of this study was to assess the correlation between the additional outcome measures and currently available neuropsychological tests that are thought to assess visuospatial construction or latent traits. This information may provide insight why a subject can perform excellently on one of the additional outcome measures of the Rey, but poorly on another.

Finally, our third aim was to combine novel outcome measures of the ROCF with lesion-symptom mapping to gain insight in the underlying neural mechanisms of these specific impairments. We expect the occipital cortex, the motor cortex and the prefrontal cortex to be involved, due to visual input processing, motor action, and executive control, respectively.

Methods

Participants:

For this study we used an existing database consisting of patients from the stroke unit of the UMC Utrecht. These patients were all admitted between November 2005 and December 2012 and met the following inclusion criteria: (1) first-ever ischemic stroke; (2) an infarction on follow-up CT or MRI; (3) complete data on the Rey-Osterrieth Complex Figure copy test. Exclusion criteria were: (1) pre-existing neurologic conditions; (2) recurrent stroke; (3) neglect; (4) hemiplegia of the dominant hand. Lesion locus and cognitive performance were no criteria for inclusion (Biesbroek et al., 2014).

Procedure

The Rey-Osterrieth Complex Figure Test was administered as part of a larger neuropsychological screening. Throughout the screening, patients were seated at a table and the ROCF was placed in front of them. Patients were asked to replicate it as accurately as possible. As mentioned earlier, the figure consists of 18 elements. A maximum of two points can be scored for each element that is correctly drawn, summing a total of 36 points. Two points are given when the element is both reproduced and placed properly. One point is scored when the element is both correct and placed poorly or when the element is distorted (or incomplete but recognizable) and placed properly. Half a point is given when the element is distorted (or incomplete but recognizable) and placed poorly. In all these cases, 'placed poorly' is defined as reproduced on an inadequate location in relation to the complete figure.

Task and Outcome measures:

Different aspects of the figure, the visuospatial construction ones, which are: (1) figure size; (2) side of omissions (left vs. right); (3) local vs. global items; and (4) location of the copied figure were examined.

Figure size

All ROCF copies were scanned and Adobe Photoshop CS6 was used for precise measurements. Figure size was measured in millimeters with one decimal by using the ruler tool. We measured the length of the circumference of the large rectangle in the replicated ROCF (in mm) and divided this number by the length of the rectangle circumference in the original ROFC, creating a variable in which: smaller than original<1<larger than original. The value of this variable ranged from 0.392 to 1.699, and it basically tells us the replicated figure's size relative to the original one. We also divided the patients in three groups based on their ratio score. Groups were defined as 'smaller replication' (0.392 through 0.899), 'equal replication' (0.9 through 1.1), or 'larger replication' (1.101 through 1.699). Figure Size was scored as 'equal replication' within a 10% deviation due to near impossibility of scoring exactly 1.0.

Side of Omissions

Number of drawn left side items vs. drawn right side items were scored using the traditional scoring system developed by Osterrieth. We divided all 18 elements in either left side or right side items (Fig. 1). The ROCF was split in the middle to make this distinction. This yielded 5 elements for scoring left side items (maximum score 10 points) and 8 elements for scoring right side items (maximum score 16 points). For each of both variables, we divided the accumulated points by the maximum obtainable points and use this ratio as variable score. The latter was necessary in order to compare the variables with one another. Conclusively, we used two variables, number of drawn left side items and number of drawn right side items, which both ranged from 0 to 1, reflecting 0 to 100% correct replication.

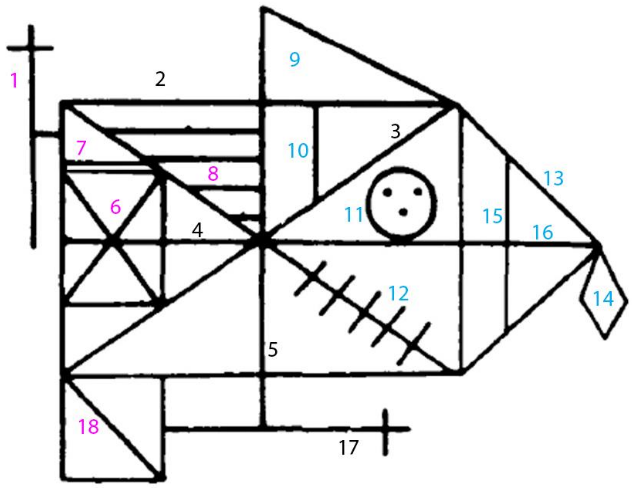

Fig. 1. Pink numbers indicate left side items, cyan numbers indicate right side items, black numbers indicate neutral items. Element 2 consists of the large rectangle that forms the central body of the figure.

<u>Local versus global items</u>

As for scoring local vs. global items, we also used the traditional scoring system developed by Osterrieth, in which we divided all 18 elements in either local or global items (Fig. 2). This yielded 12 elements for scoring local items (maximum score 24 points) and 6 elements for scoring global items (maximum score 12 points). For each of both variables, we divided the accumulated points by the maximum obtainable points and used this ratio as variable score, allowing us to compare these variables as well. As with side of omissions, this resulted in two variables: number of drawn local items and number of drawn global items, which both ranged from 0 to 1, indicating 0 to 100% correct replication.

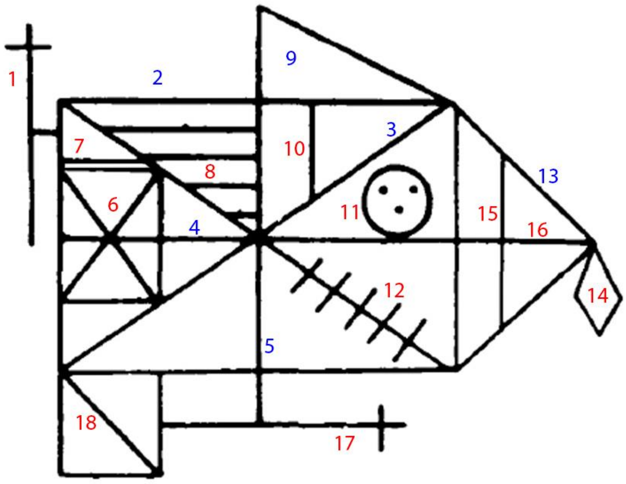

Fig. 2. Red numbers indicate local items, blue numbers indicate global items.

Figure location

Finally, the replicated figure's location on the sheet was determined using Adobe Photoshop CS6 as well. The middle of the original ROCF was measured using the ruler tool and determined at (136;99)(in mm). For each subject's copy, we then placed guidelines on both the x- and y-axes which intersected at the exact location of the original ROCF's middle. Then, also using the ruler tool, we measured the distance between the subject's ROCF copy's middle and both the guideline on the x-axis and the y-axis, yielding horizontal and vertical location values (in mm). These were used as variables for figure location. Horizontal location varied from -251 to 44.2, and vertical location varied from -252 to 65.2.

Additionally, the following outcome measures were obtained from the neuropsychological assessment:

Star cancellation test

This test consists of 52 large stars, 13 letters, 10 short words and 56 smaller stars on a page. The subject is instructed to mark all the small stars. Two central small stars have a demonstrative function, 54 stars are testable. The number of stars marked on both the left and right side were recorded. Next, the amount of marked stars on the right side is subtracted from the amount of marked stars on the left side. Hence, the score can range from -27 to 27. The test measures unilateral spatial neglect, with positive scores indicating right sided neglect and negative scores indicating left sided neglect (Halligan, J.C., & Wade, 1989).

Digit sequencing in forward order

The subject is required to repeat sequences of digits of increasing length in forward order. Score is defined as span (the amount of digits a subject is able to reproduce) multiplied by the number of correct digits. The test measures both attention and memory (Banken, 1985; Kaplan, Fein, Morris, & Delis, 1991).

Judgment of Line orientation (JULO)

This test has multiple variants. We used the original, 30-items test. The subject is shown a pair of stimulus lines and 11 reference lines. Next, he is asked to select the two reference lines with the same orientation as the stimulus lines (Benton, Sivan, Hamsher, Varney, & Spreen, 1994). The JULO measures visuospatial perception (Strauss, Sherman, & Spreen, 2006).

Rey Auditory Verbal Learning test (RAVLT)

The examiner reads aloud a total of 15 unrelated words at a rate of one word per second. The patient is asked to recall as many words as he can remember, in any given order. The procedure is carried out five times. We used the total score, that is, the sum of the items remembered in all five trials. The RAVLT measures short-term auditory memory, rate of learning and both pro- and retroactive interference (Vakil & Blachstein, 1993).

Word Fluency Test

An association task in which the subject has to write as many unique, existing words starting with a given letter as possible in limited time. The score is the amount of produced words (double and nonexistent words do not count). It is associated with attention, executive function, psychomotor speed, and memory (Cohen & Stanczak, 2000).

Voxel-based lesion-symptom mapping

Voxel-based lesion-symptom mapping is a method to analyze the relationship between brain structure and function on a voxel-by-voxel basis (Bates et al., 2003). More specifically, it analyzes the relationship between lesion location and performance on behavioral parameters, in our case our new outcome measures. Subjects are usually grouped by either lesion or behavior. In this study we focused on the 'lesion-approach', in which subjects are grouped on having either damaged or healthy brain tissue per given voxel.

Analyses:

The primary aim of this study was to assess the additional outcome measures of visuospatial and visuoconstructive processing. Here, we show which statistical tests were used and what was compared with each other.

Figure size

We assessed descriptive statistics for Figure Size. To determine whether size was significantly smaller or larger, a one sample T-test was used. We also looked at frequencies per group. Since our assumption was that the size of a replicated figure should correlate positively with higher cognitive ability, we looked at correlations between size and other neuropsychological tests (see "correlation with other neuropsychological tests").

Side of omissions

Descriptives for number of drawn left side, right side, local and global items were obtained to determine mean and SD of each group. For side of omissions, we compared ratio scores of number of drawn left side items and drawn right side items (in both cases, scores ranged from 0-1, meaning 0 to 100% correct replication). Next, we performed a paired samples t-test to compare means of left side and right side items in order to assess whether performance on these variables was different.

Local versus global features

For these variables we performed a similar analysis as the one for measuring differences in side of omissions. Descriptives were obtained to determine mean and SD of both number of drawn local items and number of drawn global items, and this was done for their ratio scores as well (again, ranging from 0-1, meaning 0 to 100% correct replication). A paired samples t-test was used to compare means between number of drawn local and global items.

Figure location

Figure location was explored by looking at two variables: horizontal and vertical location, compared to the presented ROCF figure's location. For both variables, mean and SD were obtained and a one-sample T-test was performed to assess whether figure location differed significantly from the presented figure's location. We also looked at the frequencies of displacement: how often was a figure placed more to the left, right, top or bottom? We investigated how horizontal and vertical location correlated with a bivariate correlation analysis, and in the correlation section of this paper, we investigated the correlation between these location variables and other neuropsychological tests.

Correlation with other neuropsychological tests

In order to study the relationship between performance on the ROFC and performance on other cognitive domains, we measured the correlation between our new variables and other neuropsychological tests. For each of the new outcome measures, we performed bivariate correlation tests to calculate Pearson's correlation coefficient of said outcome measure with each of the other neuropsychological tests.

Voxel-based lesion-symptom mapping

To investigate the relationship between the new outcome measures and their neural correlates voxel-based lesion-symptom mapping (VLSM) was performed for number of drawn left side items, right side items, local items and global items. For each of these outcome measures, Z-scores were obtained by using the Brunner-Munzel test (p=0.05). Next, VLSM analyses were done on z-scores for performance on the abovementioned outcome measures using Non-Parametric Mapping (univariate analysis, t-test)(Rorden & Karnath, 2004). Voxels damaged in less than 3 subjects were not tested. Correction for multiple testing was done by using Permutation Thresholding (4000 permutations, the highest the used NPM software has to offer), as a recent study implied this was the best method to correct for multiple testing (Medina, Kimberg, Chatterjee, & Branch Coslett, 2010).

Results

Demographic and stroke characteristics

For the statistical analysis of the new outcome measures, 148 patients were included (Table 1). Patients with pre-existing neurologic conditions (n=7) or recurrent stroke (n=2) were excluded. No cases of neglect or hemiplegia of the dominant hand were found.

Table 1. Demographic and stroke characteristics of the included stroke population. **A**. Education according to Verhage scoring system (scale 1-7). Time post-stroke onset in days is the average amount of days between infarction and ROCF assessment.

Demographic characteristics	
Age (SD)	63.1 (14.7)
Sex (% male)	57.7
Education (SD)[A]	4.7 (1.6)
Hand preference (%)	
Right	85.9
Left	10.1
Ambidexter	2.7
Location of ischemic lesion (%)	
Left cerebral	16.7
Right cerebral	19.3
Infratentorial	6.0
Left cerebral and infratentorial	1.3
Right cerebral and infratentorial	0.7
Left and right cerebral	0.7

Left and right cerebral and infratentorial	0.7
Missing value	54.7
Time post-stroke onset in days (SD)	7.5 (5.2)

Figure size

The value of this variable ranged from 0.392 to 1.699. Figure size was significantly larger with mean 1.07 (SD=0.21; *p*=0.001). 17.6% drew a smaller replication, 42.6% drew a roughly equal replication and 39.9% drew a larger replication.

Side of Omissions

Mean scores for number of drawn left side items (μ=6.87; SD=2.85; range 0-10) and number of drawn right side items (μ=12.91; SD=3.74; range 0-16) were obtained. Mean ratio scores for number of left-side items (μ=0.69; SD=0.28; range 0-1) and right-side items (μ=0.81; SD=0.23; range 0-1) were also obtained. Paired t-test analysis of ratio scores revealed a significant difference between number of drawn left and right side items (t=-7.24); *p*=0.001)(Fig. 3). This shows that performance on drawing left side items was inferior to performance on drawing right side items.

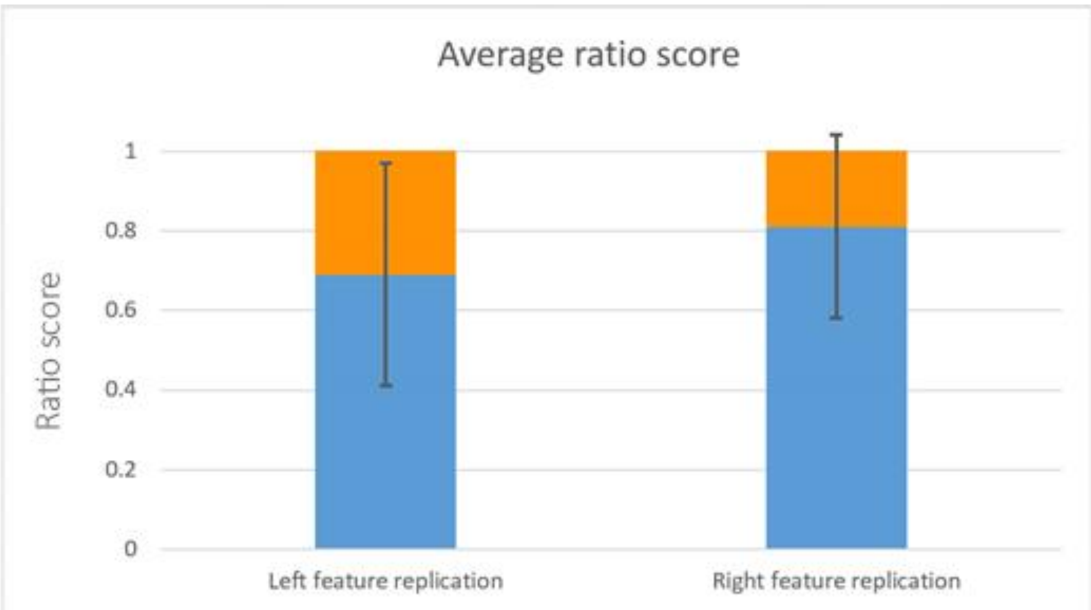

Fig. 3 Average ratio scores with SD for number of drawn left and right side items. Blue indicates below average score range, orange indicates above average score range.

Local versus global items

Mean scores for number of drawn local items (μ=18.08; SD=5.61; range 1-24) and global items (μ=9.43; SD=2.94; range 0-12) were obtained. Mean ratio scores for local items (μ=0.75; SD=0.23; range 0-1) and global items (μ=0.79; SD=0.24; range 0-1) were also obtained. Paired t-test analysis of ratio scores revealed a significant difference between number of drawn local and global items ($t=-3.00$; $p=0.003$)(Fig. 4), showing that performance on drawing local items was inferior to performance on drawing global items

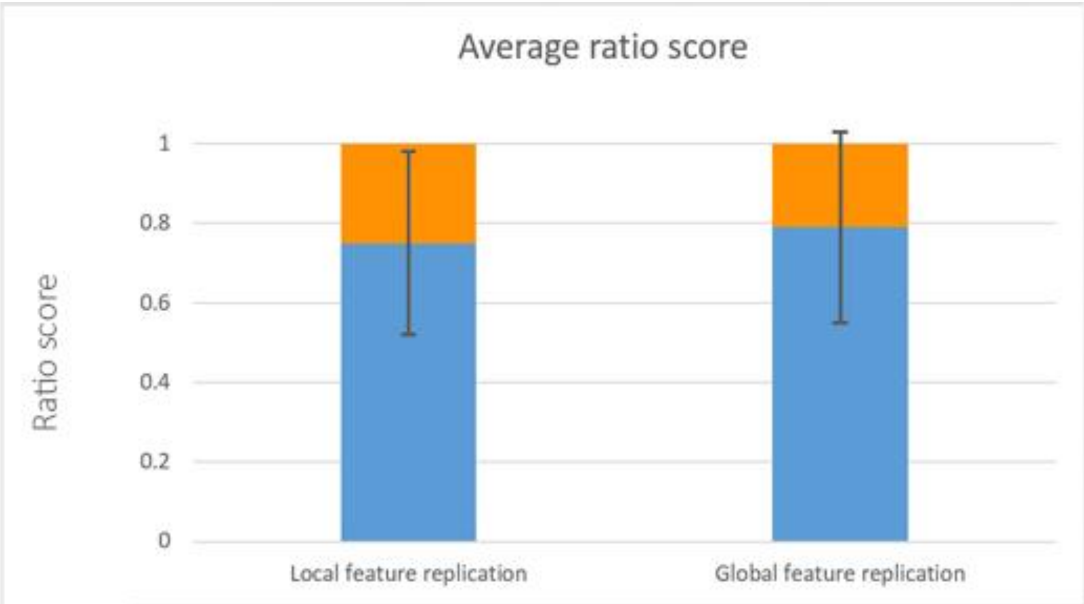

Fig. 4. Average ratio scores with SD for number of drawn local and global items. Blue indicates below average score range, orange indicates above average score range.

Figure location

Horizontal location ranged from -251.0 to 44.2 (mm). Horizontal location was significantly displaced to the left with mean -7.15 (SD=27.52; $p=0.002$). 65% drew a figure located to the left, and 35% drew a figure located to the right.

Vertical location ranged from -252.0 to 65.2 (mm). Vertical location mean (μ) was determined at 2.553 (SD=27.49) (mm). However, this displacement to the top was not significant ($p=0.262$). Furthermore, 42.4% drew the figure lower, and 57.6% drew the figure higher than the presented figure. Interestingly, bivariate correlation analysis showed a moderate positive correlation between these two location variables (0.505), suggesting that a figure drawn to the left often was drawn to the bottom, and a figure drawn to the right was commonly drawn to the top.

Correlation with other neuropsychological tests

Figure 5 gives a detailed overview of the correlations between the outcome measure of the Rey and the scores on different neuropsychological tests.

No relations were found for the measures Figure Size, Horizontal location and Vertical location and performance on NP tests. However, we did find a moderate positive correlation between horizontal location and vertical location ($r=0.505$, $p=<0.001$), indicating that a patient who draws his figure more to the right is more likely to also draw the figure towards the top of the sheet and vice versa.

The magnitude of the asymmetry score of the Star Cancellation was negatively related to the number of drawn features on both the left (-0.346) and right (-0.179) side of the Rey figure, as well as the number of drawn local (-0.267) as well as global (-0.285) features. This indicates that visuospatial construction in general is influenced negatively by unilateral neglect. The different correlations for the left and right side implies that this effect is more pronounced on the left side of a drawn figure.

Additionally, visuoperceptual abilities as measured with the JULO, working memory as measured with the Digit Span, verbal memory as measured with the RAVLT and verbal fluency were all positively related to the number of drawn features on both the left (0.442; 0.278; 0.289; 0.340) and right (0.502; 0.280; 0.328; 0.296) side of the Rey figure, as well as the number of drawn local (0.507; 0.289; 0.325; 0.332) as well as global (0.454; 0.297; 0.317; 0.351) features. This suggests that the impacts of visuoperceptual ability, working memory, verbal memory and verbal fluency are roughly equal on visuospatial construction proper.

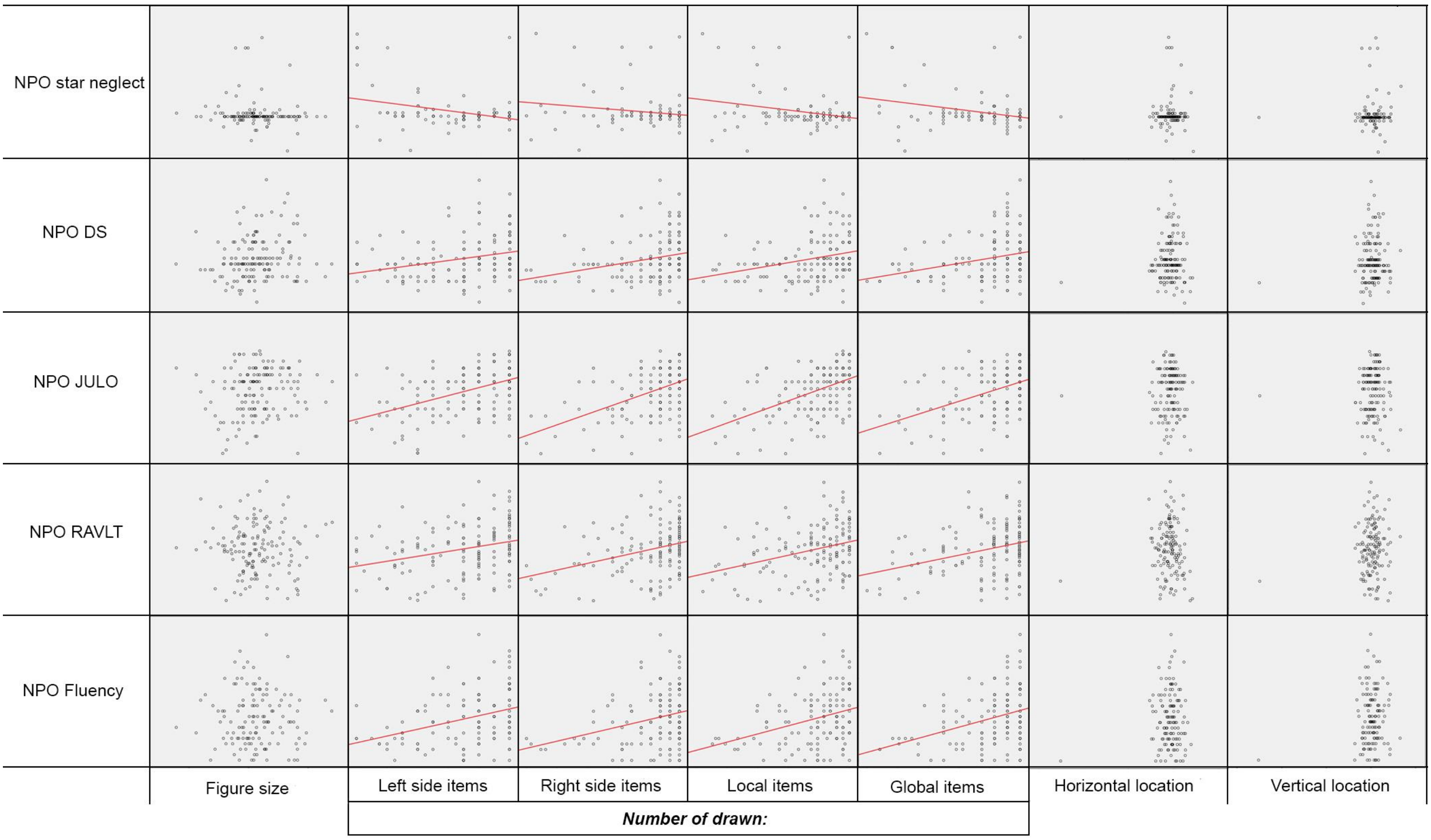

Fig 5. Panel showing scatterplots between the custom outcome measures and other neuropsychological tests. NPO DS stands for the digit sequencing test. Significant linear correlations are shown in red.

Voxel-based lesion-symptom mapping

The study cohort for lesion-symptom mapping consists of 66 patients out of the original 148 patients due to image availability (Table 3).

Table 3. Demographic and stroke characteristics for lesion-symptom mapping

Demographic characteristics	Study cohort (*n*=66)

Age, mean (SD)	59.4 (16.0)
Sex (% male)	57.6
Education, mean (SD)[a]	4.7 (1.6)
Hand preference (%)	
Right	87.9
Left	9.1
Ambidexter	1.5
Location of ischemic lesion (%)	
Left cerebral	36.4
Right cerebral	42.4
Infratentorial	12.1
Left cerebral and infratentorial	3.0
Right cerebral and infratentorial	1.5
Left and right cerebral	1.5
Left and right cerebral and infratentorial	1.5
Missing value	1.5
Time post-stroke onset in days (SD)	7.6 (5.2)

Number of drawn left-side items.

For performance on number of drawn left-side items, the Brunner-Munzel test output showed that the critical Z-value Z_c was 3.775 when using Permutation Thresholding (4000 permutations; p=0.05). The observed maximum Z-value was 7.198. VLSM analysis yielded significantly associated brain tissue, which was identified as the right insula and white matter near the right caudate nucleus (Figure 6).

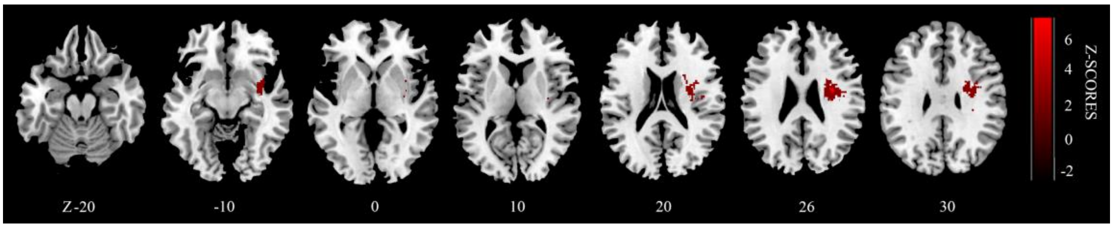

Fig. 6. VLSM results. Map of the association between the location of a lesion and replication of left sided features on the ROCF displayed on horizontal sections. Below each section its coordinate on the Z-axis is provided. Voxels exceeding the permutation threshold are displayed from dark to bright red.

Number of drawn right-side items

For performance on number of drawn right-side items, the critical Z-value Z_c was 3.719 when using Permutation Thresholding (4000 permutations; p=0.05). The observed maximum Z-value was 3.891. VLSM analysis yielded significantly associated brain tissue, which was identified as the right angular gyrus and the occipital cortex (Figure 7).

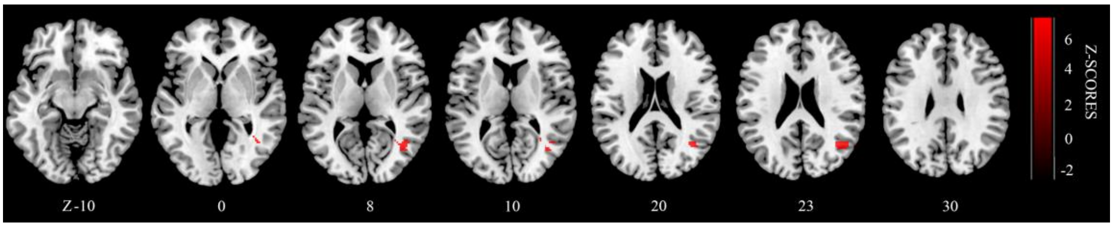

Fig. 7. VLSM results showing the association between the lesion location and replication of right sided features on the ROCF displayed on horizontal sections. Below each section its coordinate on the Z-axis is provided. Voxels exceeding the permutation threshold are displayed from dark to bright red. Voxels exceeding the permutation threshold are displayed from dark to bright red.

Number of drawn local items

For performance on number of drawn local items, the critical Z-value Z_c was 3.840 when using Permutation Thresholding (4000 permutations; p=0.05). The observed maximum Z-value was 6.790. VLSM analysis yielded significantly associated brain tissue, which was identified as the right insula and white matter adjacent to the right caudate nucleus (Figure 8).

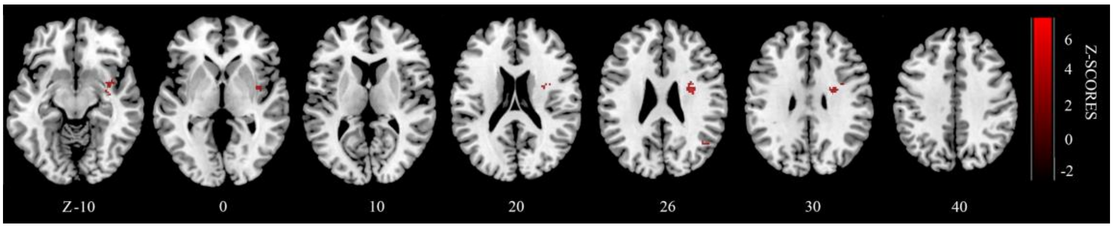

Fig. 8. VLSM results showing the association between lesion location and reproducing local features of the ROCF displayed on horizontal sections. Below each section its coordinate on the Z-axis is provided. Voxels exceeding the permutation threshold are displayed from dark to bright red.

Number of drawn global items

For performance on number of drawn global items, the critical Z-value Z_c was 3.719 when using Permutation Thresholding (4000 permutations; *p*=0.05). The observed maximum Z-value was 4.146. VLSM analysis yielded significantly associated brain tissue, which was identified as the right putamen, right angular gyrus and the occipital cortex (Figure 9).

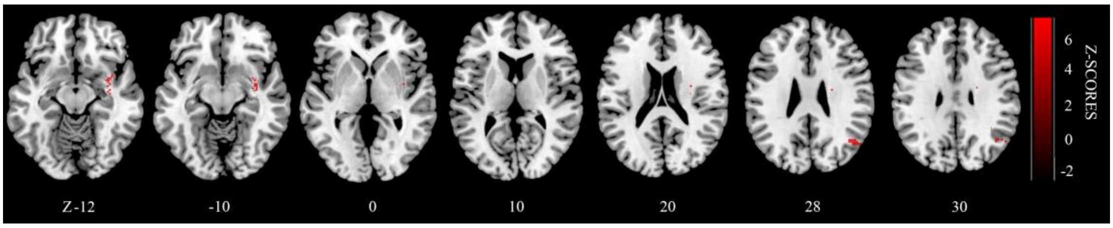

Fig. 9. VLSM results showing the association between lesion location and reproducing global features of the ROCF displayed on horizontal sections. Below each section its coordinate on the Z-axis is provided. Voxels exceeding the permutation threshold are displayed from dark to bright red.

Discussion

The aim of this study was to assess visuospatial and visuoconstructive aspects in detail, using the ROCF. More specifically, we studied figure size, number of drawn left side items, number of drawn right side items, number of drawn local items, number of drawn global items, horizontal location and vertical location. Drawn figure size was found to be significantly larger. The number of correctly drawn right-side items was significantly larger than the number of correctly drawn left-side items. Global items were drawn correctly more often than local items as well. While patients drew their figures significantly more often to the left, no significant displacement was found on the vertical axis.

Examining figure size revealed that on average, a larger figure was drawn than the original one, while the largest group drew a figure that was of roughly equal size. It remains unclear whether a larger figure size could be pathological due to lack of a control group.

As for side of omissions, results showed significantly better performance on number of drawn right-side items compared to drawn left-side items (0.81 vs. 0.69, respectively). This suggests that there is a difference in ability to replicate these elements after brain damage. This difference in performance is unlikely to be caused by hemispatial neglect due to inclusion criteria. Furthermore, lower scores on number of drawn left-side items were significantly associated with damage to the right insula and white matter near the right caudate nucleus, while lower scores on number of drawn right-side items were significantly associated with damage to the right angular gyrus and the occipital cortex.

Results regarding number of drawn and global items showed a significant difference as well: fewer local items are drawn correctly than global items (0.75 vs. 0.79, respectively). Again, this difference is not taken into account with the current scoring system. Additionally, drawing local items was associated with the right insula and white matter near the right caudate nucleus, while replicating global features was significantly associated with the right putamen, right angular gyrus and right occipital cortex.

Most patients drew their figure located to the left (65%). On the vertical plane, patients were able to place it on par with the presented figure. The location variables share a moderate correlation with one another, however. A conclusion we can draw from this is that it might be possible that instead of horizontal and vertical location being two separate variables, they are influenced by a common latent trait, e.g. a neural correlate that influences both abilities.

Correlation tests with other neuropsychological tests showed very low and insignificant correlations for both figure size and location. On the other hand, number of drawn left-side items right-side items, local items and global items showed comparable correlations with the other neuropsychological tests. These covariated in being either all positive or all negative, with raw score having the highest correlations with other tests in general. There are slight differences, however. Of all variables, number of drawn left-side itemsnumber of drawn left-side items has the highest correlation with star neglect (-0.346), as can be expected with a test that measures left-sided hemispatial neglect. Furthermore, number of drawn local items and number of drawn right-side items have a stronger correlation with the Judgment of Line Orientation task than number of drawn global items and number of drawn left-side items.

More importantly, however, is how comparable the given correlations are between the different outcome measures and the other neuropsychological tests. This basically tells us that despite the outcome measures require about equal amounts of attention, memory, psychomotor speed, executive functioning, and visuospatial perception, subjects still perform differently on them. Hence, the observed difference must be caused by another factor, which is not measured with the other neuropsychological tests. It is plausible that this difference derives from different visuospatial constructive ability. If this were true, the ROCF proves to be an excellent test to measure visuospatial construction. Osterrieth's normative standard however, would be proven inadequate of more specified assessment of visuospatial construction impairment.

Taken together, these observed differences between left, right, local and global features suggest there is more to visuospatial construction than just one general attribute, as it is currently measured. When we combined these findings with their respective neural correlates and their functions, were able to draw further conclusions.

The insula was associated with number of drawn left side items and number of drawn local items. It is primarily related to the limbic system and thought to play a role in emotional processing (Singer, Critchley, & Preuschoff, 2009), risk prediction (Preuschoff, Quartz, & Bossaerts, 2008; Singer et al., 2009), and in mediating interactions between large-scale brain networks involved in both external and internal oriented attention (Menon & Uddin, 2010). Moreover, a study conducted by Cauda et al. (2011) found two networks in which the insula is involved: one network links the insula to the temporal cortex and is mainly related to limbic regions and emotional aspects, while the second links the insula to premotor, sensorimotor, supplementary motor and middle-posterior cingulate cortices. This network suggests a role for the insula in sensorimotor integration.
In turn, this could explain why this brain area is necessary for visuospatial construction, since the latter network involves motor action guided by sensory information. In our study, this could imply that the insula allows visual information to guide motor action for drawing the ROCF. However, it does not

explain why this region is specifically associated low sores on number of drawn left side and local items, and not with number of drawn right and global items. Neither does it explain why it is associated with replicating the ROCF in general, but not with the latter two of our outcome measures.

The caudate nucleus was also associated with number of drawn left side and local items. It is believed to be involved in goal-directed action based on evaluation of action-outcomes (Grahn, Parkinson, & Owen, 2008). This assumption is strengthened by the caudate nucleus' connection to the frontal association areas. A study by Haruno and Kawato (2006) found a correlation between reward-prediction error and the caudate nucleus and ventral striatum. In another study by Potegal (1972), the author found impaired spatial orientation after small lesions of the caudate nucleus. While this doesn't show a direct link with visuospatial construction, it does indicate the caudate nucleus' involvement in spatial navigation and thus an indirect link with visuospatial construction.

The angular gyrus was associated with number of drawn right side and global items. It is thought to be associated with various tasks. According to Seghier (2013), it is involved in semantic processing, word reading and comprehension, number processing, default mode network, memory retrieval, attention and spatial cognition, reasoning, and social cognition. Moreover, Arsalidou and Taylor (2011) show that the angular gyrus is highly likely to be involved in visual-spatial attention when calculation problems are being solved. Sack (2009) noted that the angular gyrus is involved in our ability to process and integrate spatial aspects of our environment. A study by Hirnstein, Bayer, Ellison, and Hausmann (2011) investigated one such spatial cognition process: discriminating left from right. Interestingly, they found that TMS over the left angular gyrus, but not the right angular gyrus, impairs the ability to discriminate between left and right.

This is an interesting result, as our study implies damage to the right angular gyrus predicts lower scores on number of drawn right side items, but not left side items. Furthermore, the right angular gyrus was associated with global items, but not with local items. As Sack (2009) suggests the angular gyrus to process and integrate spatial aspects of our environment, it seems plausible to suggest that number of drawn global items represents more of an overview of the ROCF, as this variable represents the general figure's outlines. Especially in contrast with the local feature variable, in which specific, small elements must be replicated.

The occipital cortex was associated with both number of drawn right side items and global items. It is involved in processing visual perception. Neural signals travel from the retina to the lateral geniculate nucleus. From here, most signals are projected to the primary visual cortex – V1 – of the occipital cortex. In V1, the neural signal is further processed in the occipital cortex and ultimately projected to different brain regions via a multitude of projections (Breedlove, Watson, & Rosenzweig, 2010).

As it's relation to visuospatial construction seems obvious – it is needed to process visually perceived information – it remains a bit unclear why it is significantly associated with right side and global items, but not with left side and local items. It is likely to be involved in the latter two variables as well. A reasonable explanation for this finding would be that a functioning occipital cortex is essential for visuospatial construction, so patients with occipital cortex damage were unable to perform any visuospatial construction tasks at all, and thus were excluded from this study. On the other hand, this if this were true it does greatly reduce our power regarding speculations about occipital cortex function in this study.

The putamen was associated with number of drawn global items and is part of the basal ganglia, a structure mainly associated with voluntary movement (Bonelli & Cummings, 2007; Marchand et al., 2008). Recent research highlighted the putamen as the neural correlate of stimulus-action-reward association (Haruno & Kawato, 2006). A study by Marchand et al. (2008) found strong coactivation the putamen in both hemispheres during an unilateral motor task, suggesting that both structures are functionally integrated in unilateral movement.

A possible explanation for its involvement in number of drawn global items could thus be one of a motivational nature: the will to successfully replicate this figure in order to achieve good test results. As stated previously, the number of drawn global items variable is the only variable that focuses on the figure's main body, metaphorically 'the general figure' compared to the details, which makes it likely for a patient to focus on in order to achieve a positive test result. Marchand et al. (2008)'s finding could explain why, despite 87.9% of our study cohort being right-handed, the right putamen was involved.

A remarkable finding is that all associated brain tissue damage is found in the right hemisphere of the brain. The classical view is that the left hemisphere is associated with lingual skills and cognitive processing while the right hemisphere is associated with visuospatial processing (Kelley et al., 1998). However, some authors suggest this is an oversimplification (Corballis, 2003). Our findings are in accordance with this classical view, as all significantly related brain areas were found in the right hemisphere.

Furthermore, left side and local items share neural correlates, while right side items shares its neural correlates with global items. This suggests different neural correlates contributing to these outcome measures. In turn, this could point toward different neural correlates contributing to more specific processes within visuospatial construction, further amplifying the suggestion that visuospatial construction is not but one process, but a broad term encompassing many, complementing abilities of the brain that together shape this concept we call visuospatial construction.

There are several limitations of this study. First, there is no healthy control group. For univariate outcome measures such as figure size and location, it would be interesting to see if a control group also draws a larger figure, or a figure located more to the left. Second, while we had 148 ROCF copies from our subjects, only 66 of these subjects also had a CT or MRI image available. Since a larger sample provides larger power, it is unfortunate that this limited our power in the VLSM section. Last, we chose horizontal and vertical location as variables to determine figure location. While this is one option, there are other possibilities to determine location (e.g. a vector approach). Future research could focus on such an approach and compare the results.

Future directions regarding figure size could try an alternative approach. Figure size can be defined in different ways, as shown by Loughan et al. (2014). It would be interesting to study if size, when defined differently, yields comparable results. Moreover, a control group would allow comparison of figure size between lesioned and healthy subjects. This also applies to figure location.

As for figure location, future research should focus on a relationship between figure location as a whole instead of being split in horizontal and vertical directions, e.g., the direct distance between the original ROCF and the patient's copy. Also, it would be exciting to see whether this distance correlates with general performance on the ROCF.

Left side and local items seem to share neural correlates, as do right side and global items. Future studies could aim at deeper understanding of these neural correlates in an attempt to shed some light on how this difference can be more adequately explained.

Conclusion

Our results demonstrate that subjects can be selectively impaired on drawing items on either the left or the right side, or on a global or local scale. This difference in ability is likely caused by visuospatial construction. Moreover, left side and local item drawing ability is mediated by the insula and the caudate nucleus, while right side and global item drawing ability is mediated by the angular gyrus and the occipital cortex. Taken together, the results suggest that visuospatial construction is not a singular ability, but rather many collaborating components which can be selectively impaired. The current scoring system for the ROCF merely provides a general, total score that does not take these specific differences into account. Future research should focus on these specific differences in order to excavate the concept of visuospatial construction. In time, with better understanding of how visuospatial construction actually works, we will hopefully be able to offer better testing methods in clinical settings. In turn, this will allow for better, more specified diagnosis of patients.

Acknowledgements

I would like to thank Q. Oort for teaching me the basics of Mricron. I also would like to thank Prof. Dr. A. Postma for reviewing this thesis. Last but not least, I would like to thank Dr. E. Van den Berg and Dr. T. Nijboer for their extensive supervision and patience during this learning process.

References

Arsalidou, M., & Taylor, M. J. (2011). Is 2+2=4? Meta-analyses of brain areas needed for numbers and calculations. *Neuroimage, 54*(3), 2382-2393.

Ashton, V. L., Donders, J., & Hoffman, N. M. (2005). Rey Complex Figure Test performance after traumatic brain injury. *J Clin Exp Neuropsychol, 27*(1), 55-64. doi: 10.1080/138033990513636

Banken, J. A. (1985). Clinical utility of considering digits forward and digits backward as separate components of the Wechsler Adult Intelligence Scale-Revisd. *Journal Of Clinical Psychology, 41*, 686-691.

Bates, E., Wilson, S. M., Saygin, A. P., Dick, F., Sereno, M. I., Knight, R. T., & Dronkers, N. F. (2003). Voxel-based lesion-symptom mapping. *Nat Neurosci, 6*(5), 448-450. doi: 10.1038/nn1050

Benton, A. L., Sivan, A. B., Hamsher, K. d. S., Varney, N. R., & Spreen, O. (1994). Contributions to neuropsychological assessment. *New York: Oxford University Press*.

Biesbroek, J. M., van Zandvoort, M. J., Kuijf, H. J., Weaver, N. A., Kappelle, L. J., Vos, P. C., . . . Utrecht, V. C. I. S. G. (2014). The anatomy of visuospatial construction revealed by lesion-symptom mapping. *Neuropsychologia, 62*, 68-76. doi: 10.1016/j.neuropsychologia.2014.07.013

Bonelli, R. M., & Cummings, J. L. (2007). Frontal-subcortical circuitry and behavior. *Dialogues in Clinical Neuroscience, 9*(2).

Breedlove, S. M., Watson, N. V., & Rosenzweig, M. R. (2010). Biological Psychology, sixth edition. 281-316.

Cauda, F., D'Agata, F., Sacco, K., Duca, S., Geminiani, G., & Vercelli, A. (2011). Functional connectivity of the insula in the resting brain. *Neuroimage, 55*(1), 8-23. doi: 10.1016/j.neuroimage.2010.11.049

Cohen, M. J., & Stanczak, D. E. (2000). On the reliability, validity, and cognitive structure of the Thurstone Word Fluency Test. *Archives of Clinical Neuropsychology, 15*(3), 267-279.

Corballis, P. M. (2003). Visuospatial processing and the right-hemisphere interpreter. *Brain and Cognition, 53*, 171-176.

Grahn, J. A., Parkinson, J. A., & Owen, A. M. (2008). The cognitive functions of the caudate nucleus. *Prog Neurobiol, 86*(3), 141-155. doi: 10.1016/j.pneurobio.2008.09.004

Halligan, P. W., J.C., M., & Wade, D. T. (1989). Visuospatial Neglect: Underlying factors and test sensitivity. *The Lancet, 14*, 908-911.

Haruno, M., & Kawato, M. (2006). Different neural correlates of reward expectation and reward expectation error in the putamen and caudate nucleus during stimulus-action-reward association learning. *J Neurophysiol, 95*(2), 948-959. doi: 10.1152/jn.00382.2005

Hirnstein, M., Bayer, U., Ellison, A., & Hausmann, M. (2011). TMS over the left angular gyrus impairs the ability to discriminate left from right. *Neuropsychologia, 49*(1), 29-33.

Kaplan, E., Fein, D., Morris, R., & Delis, D. (1991). WAIS-R as a neuropsychological instrument. *San Antonio, TX: The Psychological Corporation*.

Karnath, H. O., Fruhmann Berger, M., Kuker, W., & Rorden, C. (2004). The anatomy of spatial neglect based on voxelwise statistical analysis: a study of 140 patients. *Cereb Cortex, 14*(10), 1164-1172. doi: 10.1093/cercor/bhh076

Kelley, W. M., Miezin, F. M., McDermott, K. B., Buckner, R. L., Raichle, M. E., Cohen, M. J., . . . Petersen, S. E. (1998). Hemispheric specialization in human dorsal frtonal cortex and medial temporal lobe for verbal and nonverbal memory encoding. *Neuron, 20*, 927-936.

Lange, G., Waked, W., Kirshblum, S., & DeLuca, J. (2000). Organizational strategy influence on visual memory performance after stroke: cortical/subcortical and left/right hemisphere contrasts. *Arch Phys Med Rehabil, 81*.

Loughan, A. R., Perna, R. B., & Galbreath, J. D. (2012). Does size matter? An investigation into the Rey Complex Figure in a pediatric clinical sample. *Appl Neuropsychol Child, 3*(1), 60-65. doi: 10.1080/21622965.2012.690921

Loughan, A. R., Perna, R. B., & Galbreath, J. D. (2014). Does size matter? An investigation into the Rey Complex Figure in a pediatric clinical sample. *Appl Neuropsychol Child, 3*(1), 60-65. doi: 10.1080/21622965.2012.690921

Luukkainen-Markkula, R., Tarkka, I. M., Pitkänen, K., Sivenius, J., & Hämäläinen, H. (2011). Hemispatial neglect reflected om visual memory. *Restorative Neurology and Neuroscience, 29*(5), 321-330.

Marchand, W. R., Lee, J. N., Thatcher, J. W., Hsu, E. W., Rashkin, E., Suchy, Y., . . . Steadman Barbera, S. (2008). Putamen coactivation during motor task execution. *Neuroreport, 19*(9).

Medina, J., Kimberg, D. Y., Chatterjee, A., & Branch Coslett, H. (2010). Inappropriate usage of the Brunner-Munzel test in recent voxel-based lesion-symptom mapping studies. *Neuropsychologia, 48*, 341-343.

Menon, V., & Uddin, L. Q. (2010). Saliency, switching, attention and control: a network model of insula function. *Brain Struct Funct, 214*(5-6), 655-667. doi: 10.1007/s00429-010-0262-0

Mervis, C. B., Robinson, B. F., & Pani, J. R. (1999). Visuospatial construction. *Am J Hum Genet, 65*(5), 1222-1229. doi: 10.1086/302633

Poreh, A., & Shye, S. (1998). Examination of the Global and Local Features of the Rey Osterrieth Complex Figure Using Faceted Smallest Space Analysis. *The Clinical Neuropsychologist (Neuropsychology, Development and Cognition: Section D), 12*(4), 453-467. doi: 10.1076/clin.12.4.453.7240

Poreh, A., & Shye, S. (1998). Examination of the global and local features of the ROCF using faceted smallest space analysis. *Clin Neuropsychol, 12*(4), 453-467. doi: 10.1076/clin.12.4.453.7240

Potegal, M. (1972). The caudate nucleus egocentric localization system. *Acta Neurobiology, 32*, 479-494.

Preuschoff, K., Quartz, S. R., & Bossaerts, P. (2008). Human insula activation reflects risk prediction errors as well as risk. *J Neurosci, 28*(11), 2745-2752. doi: 10.1523/JNEUROSCI.4286-07.2008

Rapport, L. J., Farchione, T. J., Dutra, R. L., Webster, J. S., & Charter, R. A. (1996). Measures of hemi-inattention on the rey figure copy for the lezak-osterrieth scoring method. *Clinical Neuropsychologist, 10*(4), 450-454.

Rorden, C., & Karnath, H. O. (2004). Using human brain lesion to infer function: a relic from a past era in the fMRI age? *Nature Reviews Neuroscience, 5*, 813-819.

Sack, A. T. (2009). Parietal cortex and spatial cognition. *Behav Brain Res, 202*(2), 153-161.

Seghier, M. L. (2013). The angular gyrus: multiple functions and multiple subdivisions. *Neuroscientist, 19*(1), 43-61. doi: 10.1177/1073858412440596

Singer, T., Critchley, H. D., & Preuschoff, K. (2009). A common role of insula in feelings, empathy and uncertainty. *Trends Cogn Sci, 13*(8), 334-340. doi: 10.1016/j.tics.2009.05.001

Stiles, J., Stern, C., Appelbaum, M., Nass, R., Trauner, D., & Hesselink, J. (2008). Effects of early focal brain injury on memory for visuospatial patterns: selective deficits of global-local processing. *Neuropsychology, 22*(1), 61-73. doi: 10.1037/0894-4105.22.1.61

Strauss, E., Sherman, E. M. S., & Spreen, O. (2006). A compendium of neuropsychological tests: administration, norms, and commentary. 811-841.

Trojano, L., Fragassi, N. A., Chiacchio, L., Izzo, O., Izzo, G., Di Cesare, G., . . . Grossi, D. (2004). Relationships between constructional and visuospatial abilities in normal subjects and in focal brain-damaged patients. *J Clin Exp Neuropsychol, 26*(8), 1103-1112. doi: 10.1080/13803390490515522

Vakil, E., & Blachstein, H. (1993). Rey Auditory-Verbal Learning Test: Structure Analysis. *Journal Of Clinical Psychology, 49*(6).