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Reproducibility of brain activation during auditory verbal hallucinations

K.M.J. Diederen [a,*], L. Charbonnier [b], S.F.W. Neggers [a], R. van Lutterveld [a], K. Daalman [a], C.W. Slotema [c], R.S. Kahn [a], I.E.C. Sommer [a]

[a] Neuroscience Division, University Medical Center Utrecht and Rudolf Magnus Institute for Neuroscience, Heidelberglaan 100, Utrecht, Utrecht, 3584 CX, Netherlands
[b] Image Sciences Institute, University Medical Center Utrecht, Heidelberglaan 100, Utrecht, Utrecht, 3584 CX, Netherlands
[c] Parnassia Bavo group, The Hague, Netherlands

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ABSTRACT

Previous studies investigated fMRI-guided repetitive Transcranial Magnetic Stimulation (rTMS) as an alternative treatment for auditory verbal hallucinations (AVH). This tailor-made treatment focuses at directing the rTMS coil to the location where hallucinatory activation is maximal, as identified with fMRI scans of individual patients. For the effective use of such treatment it is important to determine whether brain activation during AVH can be reliably detected using fMRI. Thirty-three psychotic patients indicated the presence of AVH during two subsequent scans. Reproducibility was measured by calculating 1) the distance between local maxima of significantly activated clusters and 2) percentage overlap of activation patterns over the two scans. These measurements were obtained both in single subjects and on group-level in five regions of interest (ROIs). ROIs consisted of the areas that were most frequently activated during AVH. Scans were considered reproducible if the distance between local maxima was smaller than 2 cm, as rTMS-treatment may target an area of approximately 2–4 cm. The median distance between local maxima was smaller than 2 cm for all ROIs on single-subject level, as well as on group-level. In addition, on single-subject level median percentage overlap varied between 14 and 38% for the different ROIs. On group-level, this was substantially higher with percentages overlap varying between 34 and 98%. Based on these results, AVH-scans may be considered sufficiently reproducible to be suitable for fMRI-guided rTMS treatment.

1. Introduction

The development of functional imaging techniques capable of "symptom-capturing" (i.e., capturing brain activation related to a symptom) has enabled the start of individual tailor-made treatments of psychiatric or neurological symptoms. An example of this strategy is the focal treatment of auditory verbal hallucinations (AVH) with repetitive Transcranial Magnetic Stimulation (rTMS) or experimental treatment such as invasive electrocortical stimulation. A major advantage of these tailor-made treatments is that they have the potential to treat medication-resistant symptoms such as AVH, tics, tremor or obsessions.

At present, the primary treatment for AVH consists of antipsychotic medication which is often combined with cognitive behavioral therapy. Although antipsychotic medication is largely effective in treating hallucinations, AVH do not respond to antipsychotic medication in 25–30% of schizophrenia patients. Repetitive Transcranial Magnetic Stimulation (rTMS) is a noninvasive method for altering activation of cortical neurons by rapidly changing magnetic fields. RTMS is a safe treatment method with only mild side effects such as transient headache and scalp discomfort during stimulation (Slotema et al., 2012) which may be a treatment option for AVH in patients with insufficient response to pharmacotherapy. Most studies, thus far, have applied low frequency rTMS for the treatment of hallucinations. Although the exact mechanism by which low frequency rTMS may improve AVH remains elusive, it is thought that when stimulation with rTMS is applied repeatedly, the targeted area becomes less active for a longer period, i.e., decreasing hallucinatory hyperactivation.

Although three large RCTs published recently failed to show a significant effect of rTMS in comparison to placebo-controlled treatment (Vercammen et al., 2009; Loo et al., 2010; Slotema et al., 2010), meta-analyses reported a significant effect of rTMS as compared to placebo on the treatment of AVH with mean weighted effect sizes ranging from 0.33 to 1.0 (Aleman et al., 2007; Tranulis et al., 2008; Freitas et al., 2009; Slotema et al., 2010, 2012).

Most studies applying rTMS in the treatment of AVH targeted a fixed position on the skull corresponding to the left temporoparietal area (Slotema et al., 2012). The rationale for selecting this area is that it overlies speech perception areas, hyperactivation of which has been hypothesized to be involved in the occurrence of AVH. While treatment of this area seems to result in a decrease in the severity of AVH, a number of fMRI studies showed that activation patterns during AVH tend to vary significantly among individual patients as in approximately one-half of the patients activation during AVH can be observed in right-hemispheric

* Corresponding author at: Department of Physiology, Development and Neuroscience, University of Cambridge, Downing place, CB2 3DY, Cambridge, UK. Tel.: +44 1223339544; fax: +44 1223333840.
E-mail address: kmjd2@cam.ac.uk (K.M.J. Diederen).

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areas, i.e., the right temporoparietal and inferior frontal area, homologous to Broca's area of language production (Sommer et al., 2007; Sommer et al., 2008). Initial reports from studies targeting other areas than the left temporoparietal region do, however, not show superior or even comparable effects. While Lee et al. (2005) reported reductions in severity of AVH after rTMS directed at the right temporoparietal region, this was not replicated by others (Jandl et al., 2006; Loo et al., 2010). In addition, repetitive TMS treatment of the bilateral temporoparietal regions revealed no significant differences in comparison with placebo treatment (Vercammen et al., 2009; van Lutterveld et al., 2012). Finally, stimulation of Broca's area or the left superior temporal gyrus (Schonfeldt-Lecuona et al., 2004) was no more effective than sham treatment. It should, however, be noted that the lack of efficacy of rTMS directed at more frontally located areas, such as Broca's area, might be due to the facial musculature overlying the skull in this area. Because rTMS can only reach a depth of 1–2 cm, additional muscle layers might prevent the rTMS pulse from affecting Broca's area (Hoffman et al., 2007; Slotema et al., 2012). Moreover, only few studies targeted other areas than the left temporoparietal area and the superior effects of this area as compared to other areas may result mainly from lacking power to support efficacy of rTMS targeted at other areas.

As maximum activation during AVH varies over patients a more suitable approach might be to identify areas where hallucinatory activation is maximal on a single subject-level and use these foci as the target for rTMS treatment (Sommer et al., 2007). While this tailor-made approach has proved to be feasible, only three studies have thus far investigated fMRI-guided rTMS in multiple patients of which just two studies directly compared guided to non-guided rTMS. Hoffman et al. (2007) used a design in which the first five patients were treated with rTMS targeted at three sites where hallucinatory activation was maximal or brain areas that showed significant correlation with the timecourse in Wernicke's area during AVH. In the remaining patients up to six active sites could be targeted with rTMS. Statistically greater rates of improvements in AVH were observed when rTMS was directed to left temporoparietal sites compared to anterior temporal sites and sham stimulation. Enabling a direct comparison between guided and non-guided rTMS Sommer et al. (2007) treated seven patients with guided rTMS while six patients received non-guided rTMS. Although no significant difference could be observed upon the frequency of AVH, fMRI-guided rTMS appeared superior at trend level to non-guided rTMS in decreasing severity of general psychosis. While this argues for the use of fMRI guided rTMS treatment the largest study to date revealed that the effects of fMRI-guided rTMS (and left temporoparietal rTMS) on the severity of AVH were comparable to those of sham treatment (Slotema et al., 2010). Although these results should be treated with caution, a reason for these negative findings might be that brain activation during AVH cannot be reliably detected using fMRI. This is crucial for optimal treatment as scans that are unreliable may not reflect the true substrate of interest and will therefore be less effective when used as the main source for treatment guidance. The aim of the present study was therefore to investigate spatial reproducibility of AVH-related brain activation both at the individual and at the group level. To circumvent the influence of factors that are difficult to keep constant with increased time between measurements, such as arousal, medication and caffeine-intake, reproducibility was investigated between two AVH-sessions acquired within the same visit.

2. Materials and methods

2.1. Subjects

Thirty-three psychotic patients with medication-resistant AVH were recruited from the University Medical Center Utrecht and the Parnassia Bavo Group in The Hague, The Netherlands. Patients were selected for participation from a larger group of patients with chronic hallucinations (Slotema et al., 2011) if they met the following criteria: (1) the presence of two subsequent AVH scans in which (2) intermittent AVH were experienced (i.e., AVH alternated with non-AVH state), (3) at least three AVH-episodes were present per scan (4) and AVH were indicated correctly (i.e., AVH-onsets were followed by clear offsets). Patients were diagnosed using the Comprehensive Assessment of Symptoms and History (CASH) (Andreasen et al., 1992) interview according to DSM-IV criteria by an independent psychiatrist. Demographic and clinical data of the participants is provided in Table 1.

2.2. Data acquisition

Participants indicated the presence of AVH by balloon-squeezes while scans were acquired continuously. Data acquisition was similar for all AVH-scans and took 8 min per scan. Images were obtained using a Philips Achieva 3 Tesla Clinical MRI scanner. An AVH scan consisted of a series of blood-oxygenation-level-dependent T2* weighted images over time. PRESTO-SENSE was used to acquire the T2* weighted fMRI images, optimally using parallel imaging and echo shifting to reduce acquisition time of up to 609 ms/volume (Neggers et al., 2008). Eight hundred PRESTO-SENSE images were acquired per session (40 slices, TR/TE 21.75/32.4 ms, flip angle 10°, field of view 224×256×160, matrix 64×64×40, voxelsize 4 mm isotropic, acquisition time 609 ms/volume). To improve localization of functional data, a high-resolution anatomical scan was conducted in addition to the AVH-scans (TR/TE: 9.86/4.6 ms, 1×1×1 voxels, flip angle 8°, FOV 224×160×168.00, 160 slices).

2.3. Data analysis

Preprocessing and analysis were conducted with Statistical Parametric Mapping (SPM5; Welcome Department of Cognitive Neurology, London, UK) and included the following steps: realignment, coregistration, spatial normalization and smoothing, using an 8-mm full width at half maximum Gaussian kernel. Scans were analyzed on a voxel by voxel basis using multiple regression analysis with

Table 1
Demographic data of the participants.

	Group 1: reliability analyses (N = 33)	Group 2: to define ROIs (N = 30)
	Mean	Mean
Age (years)	39.28 (SD = 10.15)	39.6 (SD = 10.01)
Age (years) at onset AVH	19 (SD = 19)	21 (SD = 11)
Gender		
Females	19	14
Males	14	16
Handedness		
Right-handed	26	26
Not right-handed	6	4
Diagnosis		
Schizophrenia	22	23
Schizo-affective disorder	3	1
Psychosis NOS	6	4
Personality disorder and psychosis NOS	1	0
Borderline personality disorder and psychosis NOS	1	1
One-time depressive period	0	1
Medication		
Antipsychotic		
No antipsychotics	4	6
Typical antipsychotics	10	7
Atypical antipsychotics	18	15
Combi typical & atypical antipsychotics	1	1
PANSS scores		
Total	67 (SD = 15)	70 (SD = 15)
Positive subscale	16 (SD = 4)	18 (SD = 4)
Negative subscale	18(SD = 5)	18 (SD = 6)

Abbreviations: AVH, auditory verbal hallucinations; N, number; SD, standard deviation; NOS, not otherwise specified; and PANSS, Positive and Negative Syndrome Scale.

one factor coding for activation (hallucination vs nonhallucination). This model was convolved with the hemodynamic response function from SPM5 to introduce typical delays of fMRI responses and fitted to the data using general linear model estimation (Worsley and Friston, 1995). Data was high-pass filtered with a cutoff of 100 s. and temporal autocorrelation was modeled with an autoregressive model of the first order (AR(1)).

2.4. Selection regions of interest

Reproducibility analyses were conducted on whole brain level and within five regions of interest (ROIs). ROIs were identified with the aid of a separate fMRI experiment in which brain activation during AVH was investigated in a group of thirty psychotic patients. The same inclusion criteria and experimental procedure was used as for the reproducibility analysis. In addition, the group included for this analysis was rather similar with respect to diagnoses and demographical characteristics to the group participating in the reproducibility analyses. Table 1 provides data on patients included in the reproducibility analyses as well as the analyses to identify the ROIs. First, a one-sample *T*-test was conducted to detect clusters displaying significant activation during AVH on group-level. Of each cluster, the most significant local maximum (i.e. voxel with the highest T-value) was identified and ROIs were then created by drawing 16 mm spheres centered on these local maxima. For this analysis, a threshold of $p = 0.05$ whole-brain false discovery rate (FDR) corrected for multiple comparisons, was used. Cluster sizes, p-values, t-values and locations of local maxima for brain activation during AVH in this group are displayed in Table 2.

This analysis revealed significant activation in five brain areas (leading to five ROIs for later reproducibility analyses) comprising the left temporoparietal region, the right inferior frontal region, the middle superior frontal region and the left motor region, as well as the right cerebellum. Activation of these regions during AVH is in concordance with previous reports (Sommer et al., 2008; Diederen et al., 2010, 2012). Activation of two of these areas, the motor region and cerebellum might be related to balloon-squeezes used to indicate the AVH (Sommer et al., 2008), rather than to the actual AVH.

2.5. Reproducibility analysis

Spatial reproducibility was measured by determining 1) Euclidian distance between local maxima and 2) Percentage overlap of significant activity between both hallucination scans. Percentage overlap '*PO*' was calculated with the Jaccard similarity coefficient (Maitra, 2010) by dividing the number of *overlapping* voxels during AVH-scan 1 and AVH-scan 2 '*AVH*1,2' by the amount of *uniquely* activated voxels for both sessions '$(AVH1 + AVH2) - (AVH1,2)$' as expressed by the formula:

$$PO = \frac{(AVH1,2)}{(AVH1 + AVH2) - (AVH1,2)} * 100.$$

Table 2
Cluster sizes, p-values, T-values and locations of local maxima for brain activation during AVH.

Regions of interests (ROIs)	MNI coordinates			z-score	p-value	Cluster size
	X	Y	Z			
Left temporoparietal area (lTP)	−52	−24	24	3.54	0.036	63
Right inferior frontal area (rIF)	56	12	4	3.42	0.037	25
Middle superior frontal area (mSF)	0	4	52	3.39	0.038	36
Left motor area (lMA)	−36	−28	52	4.11	0.024	131
Right cerebellum (rCB)	24	−52	−24	4.07	0.024	63

Threshold: $p = 0.05$ whole-brain false discovery rate (FDR) corrected for multiple comparisons.
Abbreviations: MNI, Montreal Neurological Institute.

Percentage overlap was calculated on whole brain level and within five ROIs (i.e. the five ROIs selected from a separate fMRI experiment; see selection regions of interest). Distance between local maxima was only calculated within ROIs. If multiple significant local maxima could be observed within an ROI, the local maximum with the highest T-value was selected.

Analyses were conducted on single subjects and on group-level. On single-subject level, subjects with no significant activation in at least one AVH-scan were excluded from the peak distance analysis. Individuals with no significant activation in both AVH-scans were excluded from percentage overlap analysis. This was determined with the aid of a one sample *t*-test, per scan, per subject, with a threshold of $p = 0.05$, FDR corrected for all voxels within an ROI or on whole-brain level. The same threshold was used for reproducibility analyses.

2.6. Reproducibility criterion

As rTMS may target an area of approximately 2–4 cm, scans were considered suitable for fMRI-guided rTMS-treatment if the distance between local maxima was smaller than 2 cm (Wagner et al., 2008). For more focal treatments such as invasive electrocortical stimulation and deep brain stimulation no exact criterion was specified, however, the area that may by targeted by these techniques is expected to be in the millimeter range (Miglioretti and Boatman, 2003).

3. Results

3.1. Performance data

The average number of AVH was 25 (SD 25) for the first hallucination scan and 24 (SD 34) for the second hallucination scan. The average duration of a hallucination was 13 (SD 29) seconds in scans 1 and 17 (SD 41) in scan 2, adding up to a mean total duration of hallucinations of 148 (SD 120) seconds in scan 1 and 170 (SD 178) seconds in scan 2.

No significant differences were found for the number of AVH ($T(32) = 0.41$, $p = 0.68$), the total duration of the AVH ($T(32) = -1.12$, $p = 0.27$) and the average duration of the AVH ($T(32) = -1.54$, $p = 0.14$) between the two sessions.

3.2. Amount of significantly activated voxels

Except for the left temporoparietal region the number of significantly activated voxels did not differ significantly between the two scans. On group-level, all ROIs displayed a somewhat higher number of significantly activated voxels for scan 1 compared to scan 2. This was also found on whole brain level (see Table 3).

3.3. Peak distance

3.3.1. Single-subject level

On single-subject level, distance between local maxima was below the predefined cutoff of 2 cm in all regions. It was smallest for the middle superior frontal area (2 mm), followed by the right inferior frontal area (4 mm), the cerebellum (6 mm), the left motor area (7 mm) and the left temporoparietal area (13 mm) (see Table 3 and Fig. 1).

3.3.2. Group-level

On group-level, distance between local maxima was also below the predefined criterion of 2 cm for all regions. It was 12 mm for the right inferior frontal area, 18 mm for the left motor area, 7 mm for the left temporoparietal area, 13 mm for the middle superior frontal area and 12 mm for the right cerebellum (see Table 3).

Table 3
Number of voxels significantly activated in the two AVH-scans, percentage overlap and distance between local maxima for the two AVH-scans.

	N voxels1		N voxels2		Statistics	% Overlap		Peak distance	
	Median	Range	Median	Range	N voxels 1 vs N voxels 2	Median	Range	Median	Range
Single-subject									
lTP	137	9–243	74	1–240	$Z=-2.930$, $p=0.003^*$	31%	0–97%	13 mm	0–22 mm
lMT	134	10–220	90	0–220	$Z=-0.237$, $p=0.813$	23%	0–68%	7 mm	0–22 mm
rIF	68	0–161	71	0–166	$Z=-0.168$, $p=0.866$	25%	6–68%	4 mm	0–19 mm
mSF	111	0–242	117	0–244	$Z=-0.264$, $p=0.792$	38%	0–96%	2 mm	0–23 mm
rCB	70	3–237	109	11–242	$Z=-1.354$, $p=0.176$	14%	0–96%	6 mm	0–17 mm
WB	600	5–6121	300	6–6926	$Z=-0.884$, $p=0.376$	22%	0–61%		
	Total		Total			Total		Total	
Group-level									
lTP	207		136			82%		7	
lMT	221		192			95%		18	
rIF	147		138			98%		12	
mSF	161		105			76%		13	
rCB	193		83			63%		12	
WB	7304		2560			34%			

Abbreviations: lTP, left temporoparietal area; lMT, left motor area; rIF, right inferior frontal area; mSF, middle superior frontal area; rCB right cerebellum; WB, whole brain and N, number.

3.4. Percentage overlap

3.4.1. Single-subject level

On single subject-level, median percentage overlap was highest for the middle superior frontal area (38%), followed by the left temporoparietal area (31%); the right inferior frontal area (25%), the left motor area (23%), whole brain (22%) and the right cerebellum (14%) (see Table 3 and Fig. 2).

3.4.2. Group-level

On group-level, percentage overlap was 98% for the right inferior frontal area, 95% for the left motor area, 82% for the left temporoparietal area, 76% for the middle superior frontal area, 63% for the right cerebellum and 34% on whole brain level (see Table 3 and Fig. 3).

4. Discussion

This study investigated spatial reproducibility of brain activation during auditory verbal hallucinations (AVH) to evaluate whether symptom capture scans can be used for fMRI-guided tailor-made focal treatments. Reproducibility was assessed with distance between local maxima and percentage overlap as the main measurements.

The median distance between local maxima was smaller than 2 cm for all ROIs on single-subject, as well as on group-level. In addition, on single subject level, percentage overlap was between 14 and 38% in all regions of interest (ROIs). On group-level, this was much higher with a percentage overlap of 98% in the most reproducible ROI.

Based on our criterion for reproducibility of less than 2 cm distance between the local maxima, these scans can be considered suitable for fMRI-guided rTMS-treatment. However, it is important to note that in the left temporoparietal area, which corresponds with the region most frequently targeted in the treatment of AVH (Slotema et al., 2010), over 25% of individuals displayed a median distance of more than 2 cm (see Fig. 1) between local maxima. Furthermore, the median percentage overlap was below 40% in all ROIs. In addition, our measure of individual variability should be seen as a lower bound of reproducibility, as in this study reproducibility was investigated between two AVH-scans acquired within the same fMRI session to circumvent the influence of factors that are difficult to keep constant with increased time between measurements, including arousal, medication and caffeine-intake.

Although we did not set criteria for other focal treatments such as invasive electrocortical stimulation it is highly questionable if hallucination scans can be considered suitable for guiding these treatments as the areas that may be targeted by these techniques are expected to be within the millimeter range (Miglioretti and Boatman, 2003).

This is the first study to investigate reproducibility of AVH-related brain activation. However, fMRI-reliability was previously studied in relation to motor and visual tasks, as well as during various cognitive

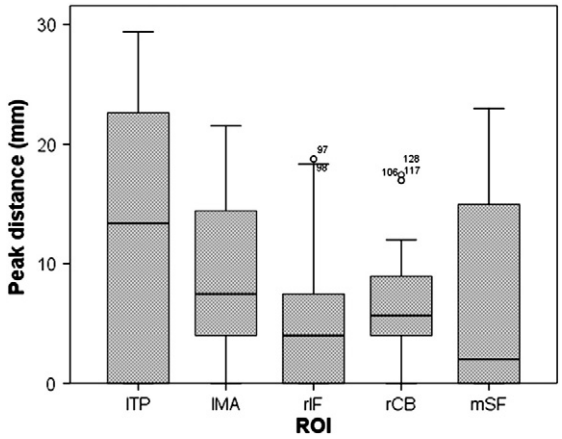

Fig. 1. Within-subject distance between significant local maxima in scan 1 versus scan 2. Abbreviations: lTP, left temporoparietal area; lMT, left motor area; rIF, right inferior frontal area; mSF, middle superior frontal area and rCB right cerebellum.

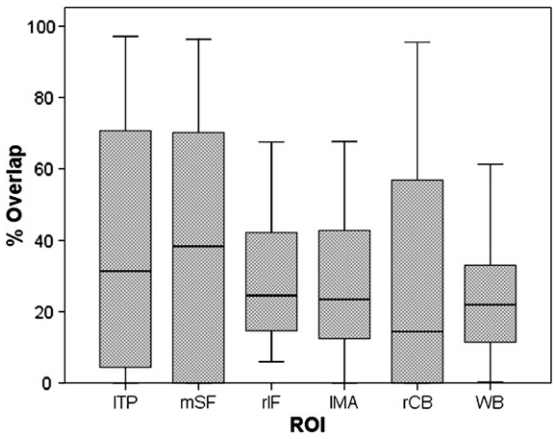

Fig. 2. Within-subject percentages overlap. Abbreviations: lTP, left temporoparietal area; lMT, left motor area; rIF, right inferior frontal area; mSF, middle superior frontal area; rCB right cerebellum and WB, whole brain.

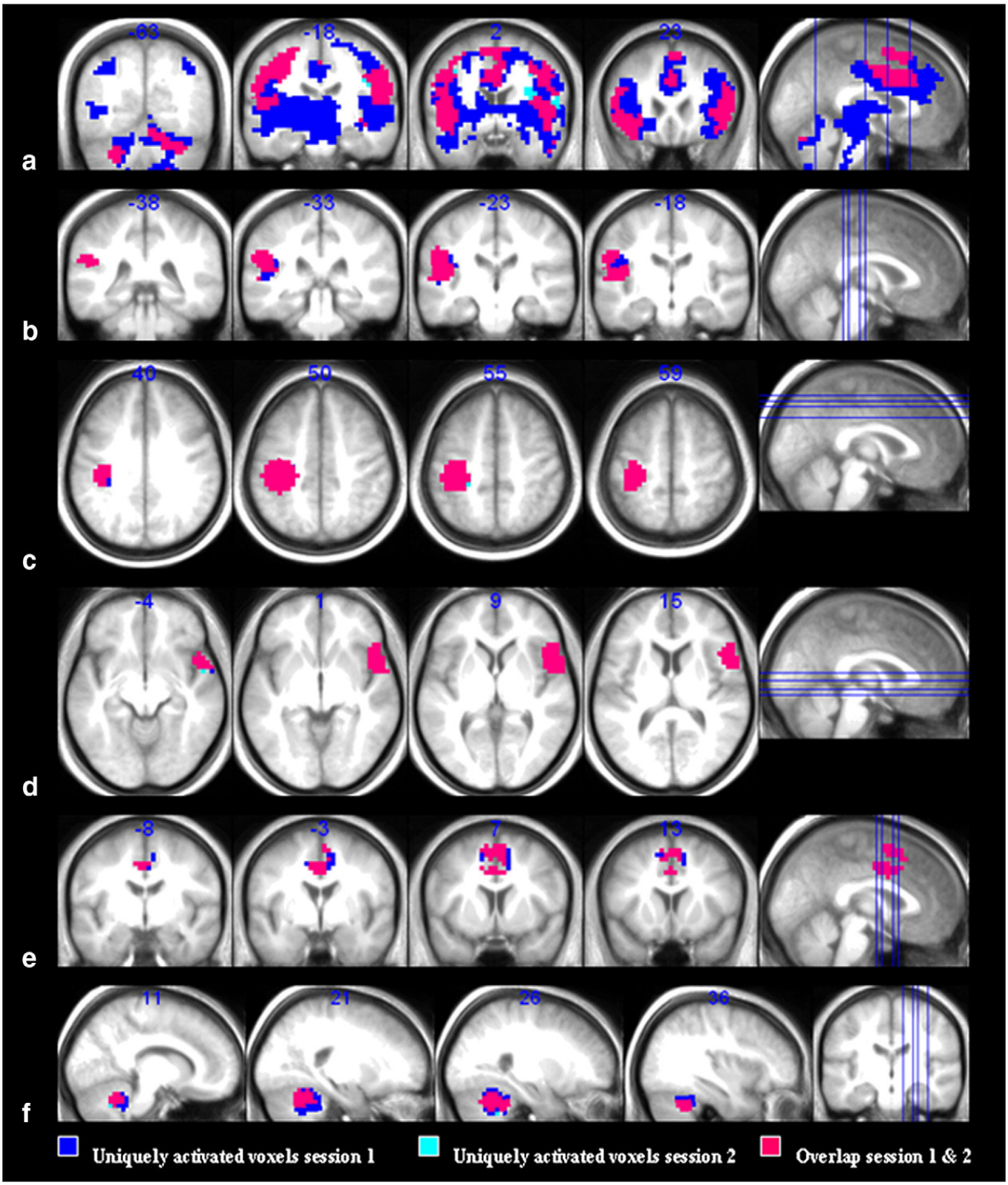

Fig. 3. Brain regions significantly activated on whole brain level and within ROIs in AVH-scan 1 and AVH-scan 2 of the group-wise analysis. a. Whole brain, b. left temporoparietal area, c. left motor area, d. right inferior frontal area, e. Middle superior frontal area and f. right cerebellum. Threshold: $p = 0.05$, false discovery rate corrected for multiple comparisons within ROIs or on whole-brain level.

tasks (Rombouts et al., 1998; Tegeler et al., 1999; McGonigle et al., 2000; Manoach et al., 2001; Raemaekers et al., 2007; Zandbelt et al., 2008; Bennett and Miller, 2010). While percentage overlap is frequently used to investigate reproducibility, distance between local maxima is not a standard measure. Recently, Bennett and Miller (2010) reviewed fMRI-reliability studies and reported an average percentage overlap, calculated with the Jaccard coefficient, of 33% when the test and retest scans took place within the same hour. This is rather similar to the percentage overlap observed in this study which ranged between 14 and 38% on single-subject level. Bennett and Miller (2010) also showed that most studies observed a higher percentage overlap on group-level than on single-subject level which is in line with the findings of the current study.

4.1. Limitation

The main limitation of the metrics employed in this study, especially percentage overlap, is the dependence on the selected significance threshold (Manoach et al., 2001). Moreover, with respect to the reproducibility criterion adopted for rTMS a limitation is that the size of the

area targeted by rTMS depends on a number of factors including coil geometry and orientation (Kammer et al., 2007). As a result, our criterion of 2 cm might be appropriate for the most commonly used coils, namely the fig. of 8 coil, but not for others such as the H-coil.

5. Conclusion

In summary, as the median distance between local maxima on individual scans was smaller than 2 cm in all ROIs, these scans may be considered sufficiently reproducible and hence suitable for fMRI-guided rTMS treatment. These results should, however, be treated with caution as reproducibility was measured within one scan session and may therefore represent a lower bound of reproducibility. For invasive electrostimulation, however, higher percentage of overlap and lower medium distance between local maxima are required.

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Contributors

KMJ Diederen and L Charbonnier designed the study, processed and analyzed the data, and wrote the manuscript. R van Lutterveld, K Daalman and CW Slotema contributed to the collection and interpretation of the data and edited the manuscript. SFW Neggers, RS Kahn and IEC Sommer supervised the study, edited the manuscript and were involved in the study design. All authors contributed to and have approved the final manuscript.

Conflict of interest

The authors have no conflicts of interest to report.

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