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Structural changes in brain morphology induced by brief periods of repetitive sensory stimulation

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ABSTRACT

There is a growing interest in identifying the neural mechanisms by which the human brain allows for improving performance. Tactile perceptual measurements, e.g. two-point discrimination (2ptD), can be used to investigate neural mechanisms of perception as well as perceptual improvement. Improvement can be induced in a practice-independent manner, e.g. in the tactile domain through repetitive somatosensory stimulation (rSS). With respect to tactile perception, the role of cortical excitability and activation within the somatosensory cortex has been investigated extensively. However, the role of structural properties, such as regional gray matter (GM) volume, is unknown. Using high resolution imaging and voxel-based morphometry (VBM), we sought to investigate how regional GM volume relates to individual 2ptD performance. Furthermore, we wanted to determine if electrical rSS has an influence on regional GM volume.

2ptD thresholds of the index fingers were assessed bilaterally. High-resolution (1 mm^3), T1-weighted images were obtained using a 3T scanner pre-and post-stimulation. RSS was applied for 45 min to the dominant right hand, specifically to the fingertips of all fingers.

At baseline, performance in the 2ptD task was associated with regional GM volume in the thalamus, primary somatosensory cortex, and primary visual cortex (negative association). After 45 min of rSS, we observed an improvement in 2ptD of the stimulated hand, whereas no improvement in tactile performance was seen on the non-stimulated side. These perceptual changes were accompanied by an increase in GM volume in the left somatosensory cortex and the degree of improvement correlated with GM volume changes in the insular cortex.

Our results show that structural changes in the brain, specifically in regions receiving afferent input from the stimulated body site can be induced via a short-term intervention lasting only 45 min. However, the neurobiological correlates of these changes and the dynamics need to be further elucidated.

Introduction

Apart from identifying the neural correlates of tactile perception and perceptual decision-making, there is an increasing interest to identify the mechanisms by which participants improve their perceptual abilities. On a cortical level, mechanosensory information is considered to be processed in a hierarchical manner, where the primary somatosensory cortex (SI) serves as the main sensory recipient area for the sense of touch. Processing of somatosensory inputs beyond the SI occurs in several adjacent areas, such as the posterior parietal cortex, the supramarginal gyrus (Kim et al., 2014) and the insular cortex (Coghill et al., 2001), which are thought to be involved in both higher-level processing

Abbreviations: 2ptD, two-point discrimination; BA, Brodmann Area; D2, index finger; FWE, family-wise error; GLM, general linear model; GM, gray matter; IC, insular cortex; rSS, repetitive sensory stimulation; NMDA receptor, N-methyl-D-aspartate receptor; SI, primary somatosensory cortex; SII, secondary somatosensory cortex; SPM, statistical parametric mapping; VBM, voxel-based morphometry.

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as well as multimodal integration. Both lesion, as well as imaging studies, suggest that the SI is essential for touch sensation, while the posterior parietal cortex, the supramarginal cortex and insular cortex (IC) play an important role in higher cognitive tasks such as shape, texture and object recognition (Burton and Sinclair, 2000; Kim et al., 2014; Pleger et al., 2003; Preusser et al., 2015).

Improvement in perceptual performance is usually achieved by training and practice (Seitz and Watanabe, 2005; Seitz and Dinse, 2007); however, improvement can also be induced in a training-independent manner, e.g. through repetitive somatosensory stimulation (rSS) (Beste and Dinse, 2013; Godde et al., 2000; Seitz and Watanabe, 2005; Seitz and Dinse, 2007). For example, several studies have shown that rSS applied to the index finger improves tactile two-point discrimination (2ptD) of that finger, presumably via functional reorganization within the somatosensory cortex (Dinse et al., 2003; Freyer et al., 2012; Godde et al., 2000; Pleger et al., 2003, 2001). Using functional brain imaging, Pleger et al. demonstrated that rSS applied to the right index finger led to an enlargement of the regions representing the stimulated finger in primary and secondary somatosensory cortices (SI and SII). Additionally, they demonstrated that the degree of individual enlargement in the SI correlated with the individual decrease in discrimination thresholds (Pleger et al., 2003). Importantly, these effects were side-specific, such that the contralateral hand, which had not been stimulated, remained perceptually and cortically unaffected (Dinse et al., 2003; Godde et al., 2000; Heba et al., 2016; Pleger et al., 2001).

In general, functional neural correlates of tactile learning, whether through sensory stimulation or through task training, have been investigated extensively within the somatosensory cortex (Elbert et al., 1995; Haag et al., 2015; Harrar et al., 2014; Heba et al., 2016; Kolasinski et al., 2016; Pleger et al., 2003; Ragert et al., 2004; Vidyasagar et al., 2014). In contrast, little is known about the changes in brain structure associated with tactile perception and tactile learning. Erpelding et al. found an association between cortical thickness in the primary somatosensory cortex and thermoception in terms of warm-detection thresholds, as well as heat- and cold-pain thresholds (Erpelding et al., 2012). Conde et al. reported that the regional cortical thickness of the sensorimotor cortex was correlated with the amount of excitability changes induced by 10 min of a paired associative stimulation (PAS, facilitatory protocol). However, no associations with behavioral parameters were reported (Conde et al., 2012).

In previous studies, we have demonstrated that low-frequency BOLD fluctuations within the representational field of the hand correlated with baseline two-point discrimination. We also demonstrated that local concentrations of the inhibitory neurotransmitter gamma-amino-butyric acid (GABA) predicted improvement in 2ptD performance following rSS intervention (Haag et al., 2015; Heba et al., 2016). We extend these studies here by asking whether there is a relation between gray matter (GM) volume within the tactile perception network and 2ptD thresholds at baseline and whether improvement in tactile perception following electrical rSS had an effect on observed GM volume. Using high resolution (1 mm^3) structural images and voxel-based morphometry, we sought to investigate (i) how regional gray matter volume relates to 2ptD performance, and (ii) if 45 min of rSS have, apart from the behavioral effect, an influence on local brain morphology in terms of an increase or decrease in regional gray matter volume.

Experimental procedures

Participants and behavioral measures

Twenty-four right-handed healthy subjects participated in this study. Five participants were excluded from further analysis due to either excessive movement in the scanner, incomplete data, or use of medication. Thus, 19 participants (11 men, 8 women; aged 24 ± 3.8 years; for more details see Table 1) were included in the analysis, all of whom fell within the normal range of depression and trait anxiety levels, as assessed using the Beck Depression Inventory (BDI) and State-Trait Anxiety Inventory (STAI) (Spielberger et al., 1983), respectively. Data acquired in this study has previously been reported with respect to BOLD fluctuations (Haag et al., 2015) and edited spectroscopy of GABA (Heba et al., 2016). For all study participants, also high resolution (1 mm^3) T1-weighted images had been acquired (subject to the current analyses). The study was performed in accordance with the Declaration of Helsinki and has been approved by the local ethics committee of the Ruhr-University Bochum. Prior to enrollment, study participants gave written, informed consent.

Table 1
Behavioral data.

Gender	11 males/8 females	mean	range	SD
Age		24.1	19–32	3.7
2-point discrimination	dom baseline	1.59	1.41–1.83	0.13
	dom post-rSS	1.39	0.95–1.75	0.22
	dom gain (%)	12.67	−6.18–46.01	12.24
	nondom baseline	1.51	1.18–1.83	0.19
	nondom post-rSS	1.5	1.00–1.94	0.27
	nondom gain (%)	−0.01	−26.75–34.06	15.42

Abbreviations: SD = standard deviation, dom = dominant (right) hand, nondom = non-dominant (left) hand.

Two-point discrimination thresholds

2-point discrimination (2ptD) performances were assessed on the tip of the index finger (D2) of both hands by using the method of constant stimuli (Dinse et al., 2005; Kalisch et al., 2009). The two assessments took place outside the scanner (after the MRI scans prior and after rSS). A custom-made device (see Fig. 1) was used to measure the 2ptD semi-manually at a fixed location on the skin of the fingertips by rapidly switching between stimuli. The stimuli consisted of seven pairs of brass needles with individual spacing (ranging from 0.7 to 2.5 mm in increments of 0.3 mm) and a single needle as zero distance (control condition). Brass pins were 0.7 mm thick with blunt tips of approximately 200 μm in diameter. Tactile stimuli were applied for approximately 1 s with application forces ranging between 150 and 200 mN. The participants were instructed to place their finger on the support and to maintain this initial position of the finger throughout the experiment. Probes were presented 8 times in a pseudo-randomized order resulting in 64 trials (8 blocks, each block of a randomized order of the 7 distances and the control condition, the same order for all subjects within a session) (Godde et al., 2000; Pleger et al., 2001) Participants were not informed about the ratio of paired to single needles being 7:1. The participants had to decide immediately after stimulus contact if they had the sensation of one or two needles being applied; they had to report the percept of a single needle (or any ambiguous stimulus) as “1” and the distinct percept of two needle tips as “2”. A recent publication by a member of our group showed that there are substantial serial order effects in the type of two-point discrimination task that was used here (Thiel et al., 2014). Therefore, to minimize additional interindividual variance evoked by individual serial order effects resulting from individual randomization, we decided to use the same randomization for all participants. The device was used by the same investigator to reduce inter-observer confounds and pressure differences between trials. However, anticipation and back-tracking of the participants can potentially influence the measurements to some degree. The tip spacing was plotted against the percentage of double-tip responses given and fitted by a binary logistic regression, resulting in a psychometric function where the 50% correct level of the sigmoid fit marked the individual 2ptD threshold. All participants underwent one training session in order to familiarize themselves with the testing procedure.

Electrical repetitive sensory stimulation protocol

RSS was applied for 45 min to the dominant right hand, i.e. to the

Fig. 1. A Custom-made device for measuring 2-point discrimination thresholds of the fingertips (Dinse et al., 2005; Kalisch et al., 2009).

fingertips of all digits and consisted of stimulus trains lasting 2 s (including 2 × 0.5 s ramps, single-pulse duration: 0.2 ms (square), frequency: 20 Hz) and inter-train intervals of 5 s, delivered from a digital storage that triggered a standard TENS device (Pierenkemper, Germany). Electrical pulses were transmitted via surface electrodes (4 cm^2, Pierenkemper) attached to the first and third segment of each finger (cathode placed proximal); current intensity was adjusted individually for each participant (mean intensity 9.48 ± 3.37 mA) to maintain a stable percept of stimulating the fingertips of the dominant hand across participants. During stimulation, participants were allowed to move around.

MRI protocol

Participants were scanned in a Philips 3.0 T Achieva X-series scanner using a 32-channel head coil. High-resolution, T1-weighted, structural images (MPRAGE, TR/TE: 8.5/3.9 ms, flip angle 8°, voxel size (1 mm^3) isotropic, field of view 240 × 240 × 220 mm) were acquired. Images were transferred from the scanner to a Linux work station (Ubuntu 14.04 LTS) and converted from DICOM to NIfTI format.

Image preprocessing and statistical analysis

Preprocessing of structural images for the VBM analyses was performed using the VBM8 toolbox (VBM8, http://dbm.neuro.uni-jena.de/vbm/) within SPM8 (Wellcome Trust Centre for Neuroimaging, University College, London, UK) running under MATLAB R2016b (Mathworks). The preprocessing steps involved spatial normalization to the same stereotactic space (using the DARTEL algorithm implemented in SPM8), segmentation and spatial smoothing (Gaussian kernel of 8 mm full-width at half maximum for GM images). Modulated images were used for statistical analyses; correspondingly, GM values are referred to as regional GM volume (Good et al., 2001). We chose the modulation option correcting for non-linear warping only since it is recommended for changes in relative volumes, already corrected for brain size, as done in our study. To avoid possible edge effects around the border between gray and white matter and to include only relatively homogenous voxel, we excluded all voxels with an absolute intensity value of <0.1 (of a maximum value of 1) (Gerber et al., 2014; Luders et al., 2013).

Voxel-wise statistics were performed in the framework of the general linear model (GLM) implemented in SPM8. In a first step, we performed regression analyses, using the multiple regression model implemented in SPM8, to identify brain regions where the independent variable (performance; i.e. 2ptD at baseline and after rSS) predicted GM volume. Age was added as a covariate of no interest in all models. We then conducted a paired *t*-test to compare GM volume prior and after the application of rSS to detect changes in GM volume associated with the intervention. Finally, we performed a regression analysis with change of performance (Δ 2ptD) and change of GM volume (using the difference images calculated with the 'Imcalc' function implemented in SPM), to identify brain regions where the change in performance predicted the change in regional brain morphology.

Corrections for multiple comparisons were performed as follows: statistical parametric maps were thresholded at $p < 0.001$ (uncorrected, voxel-level, with 50 contiguous voxels) (Driemeyer et al., 2008). In a first whole-brain analysis (exploratory) results were corrected for multiple comparisons throughout the whole brain ($p < 0.05$, cluster-level corrected, using family-wise error (FWE) correction). In a second set of analyses we allowed for a more liberal threshold, applying FWE corrections within brain regions previously described to be involved in tactile perception (ROI-based correction for multiple comparisons): the thalamus, the postcentral gyrus, the IC and the posterior parietal cortex (Kim et al., 2014; Pleger et al., 2003; Preusser et al., 2015). ROI-masks for each region were created using the WFU-Pickatlas and the AAL-template. Clusters were deemed significant when they survived FWE correction (cluster-level $p < 0.05$) within these predefined regions. Other clusters surviving the initial threshold (voxel threshold $p < 0.001$ uncorrected, 50 contiguous voxels) anywhere else in the brain are reported, as they might be of some interest to future investigations.

Finally, we used the GM eigenvariates derived from the clusters identified by the longitudinal analysis to perform structural connectivity analysis. Correlation of anatomical features of brain regions (e.g. regional GM volume) across individuals may indeed reflect functional interactions among these regions. This approach has been applied in the context of various diseases and has recently been extended to the analysis of whole brain networks based on GM parameters (Labus et al., 2014; Rüsch et al., 2007). From the longitudinal analysis we extracted the GM difference values from the clusters identified in the paired *t*-test, i.e. in the secondary somatosensory cortex (OP4), the hippocampus, the postcentral gyrus and the amygdala (Table 3). We then tested whether changes in GM were correlated with each other. A positive correlation indicates that the intervention affects different regions to the same degree, i.e. a strong increase in GM in region A is associated with a strong increase in region B, suggesting that both regions, despite spatial remoteness, form a network.

Anatomical labeling of brain regions showing either significant associations between performance and GM volume or significant differences between pre- and post-rSS was performed using the SPM extension Anatomy Toolbox (Eickhoff et al., 2005). Visualization of VBM results

was performed using MRIcroGL (http://www.cabiatl.com/mricrogl/). MATLAB 2016b (Mathworks) was used to plot changes in performance (Fig. 2) and the association between change in performance and change in GM (Fig. 5b).

Results

Tactile performance

The 2ptD thresholds of the right index finger ranged from 1.41 to 1.83 mm (1.59 ± 0.13 mm) at baseline and from 0.95 to 1.75 mm (1.39 ± 0.22 mm) after the application of rSS. The 2ptD thresholds of the left index finger ranged from 1.18 to 1.83 mm (1.51 ± 0.19 mm) at baseline and from 1.00 to 1.94 (1.5 ± 0.27) after the application of rSS (Table 1 and Fig. 2). No gender differences were seen in 2ptD thresholds of the right ($t = 0.70$, $p = 0.50$) or the left ($t = 1.1$, $p = 0.28$) hand. These values are within the range reported by previous studies (Haag et al., 2015; Heba et al., 2016; Ragert et al., 2008). 2ptD of the index fingers were highly correlated (before rSS: $r = 0.7$ $p = 0.001$, and after rSS: $r = 0.52$, $p = 0.024$). A repeated-measures ANOVA with two factors (site x time) showed a significant interaction of these factors ($F_{1,18} = 13.389$, $p < 0.001$) (Fig. 2): post hoc t-tests revealed that 2ptD thresholds of the stimulated dominant hand decreased significantly ($t = 4.378$, $p < 0.001$) while the non-stimulated non-dominant hand remained unaffected by rSS ($t = 0.104$, $p = 0.92$).

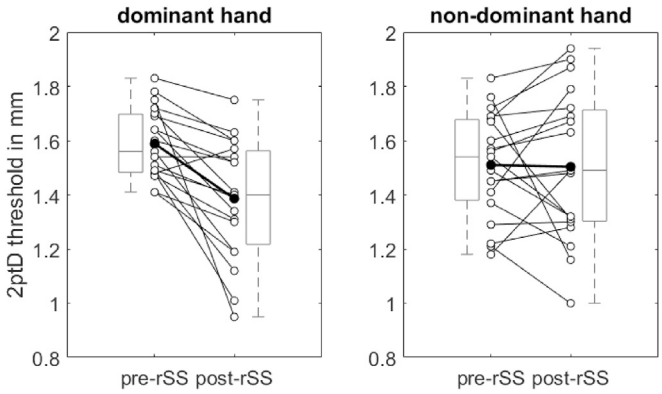

Fig. 2. Boxplots and line-plots for the two-point discrimination thresholds of the index fingers of each hand before and after rSS. White markers show the within-subject changes of 2ptD from pre-to post-rSS. Black markers show the mean change of 2ptD from pre-to post-rSS.

Voxel-based morphometry – regression analyses

The 2ptD thresholds of the dominant hand were used as predictors with regional GM volume before and after the rSS as dependent variables, and age as a covariate of no interest. At baseline, the explorative whole-brain analysis ($p < 0.05$, FWE-corrected) found a positive association between 2ptD thresholds and GM volume in the left visual cortex (Table 2 and Fig. 3a; $p = 0.03$, FWE-corrected, peak coordinates: $x = -27$, $y = -61$, $z = -2$; $k = 627$ voxels); i.e. the higher the 2ptD threshold (the weaker the performance), the higher the GM volume.

Two clusters displaying a negative association between 2ptD thresholds and GM volume were found (significant for multiple comparisons within ROI analyses): in the left thalamus ($p = 0.031$, peak coordinates: $x = -20$, $y = -28$, $z = 10$; $k = 31$ voxels) and in the left postcentral gyrus (SI), including parts of BA 1, 3b and 4a (Table 2 and Fig. 3a; $p = 0.022$, peak coordinates: $x = -24$, $y = -39$, $z = 69$; $k = 178$ voxels), i.e. the lower the 2ptD threshold (the better the performance), the higher the GM volume. However, this latter association was also found after rSS (Table 2 and Fig. 3b; $p = 0.03$, peak coordinate: $x = -26$, $y = -34$, $z = 63$; $k = 191$ voxels).

Voxel-based morphometry – longitudinal analysis

To detect changes in GM volume over time a paired *t*-test was performed, comparing regional GM volume before and after rSS. The paired *t*-test revealed a significant increase in GM volume in the left parietal operculum (Table 3 and Fig. 4; $p = 0.03$, FWE corrected, peak coordinates: $x = -62$, $y = -12$, $z = 18$; $k = 301$ voxels) involving parts of the SII, subregion 4 (OP4) and BA 3b as determined by the Anatomy Toolbox (Eickhoff et al., 2005).

Furthermore, another cluster (Fig. 4; $x = -36$, $y = -28$, $z = 40$; $k = 66$) displaying an increase in GM volume was found in the left postcentral gyrus (BA: 2, 3a, 3b), projecting to the representational field of the right hand ($x -48$, $y = -34$, $z = 46$) (Kim et al., 2014). Of note, this cluster did not survive correction for multiple comparisons within the postcentral gyrus. However, with respect to the representational field of the right hand serving as the primary input channel of rSS to the cortex, we had a strong *a priori* hypothesis for this rather confined area within the primary somatosensory cortex. Against this background, we will briefly discuss the finding in the discussion section.

Outside the somatosensory system, there were two more clusters (voxel level: $p<0.001$, $k>50$ voxels), one displaying an increase in regional GM in the left hippocampus (CA1, CA2), and one displaying a decrease in GM in the right amygdala.

Correlations of GM changes (post-pre) within the identified clusters revealed a positive correlation between GM in the secondary

Table 2
Regressions with two-point discrimination thresholds and regional gray matter volume before and after repetitive sensory stimulation.

Multiple regression Predictor variable: 2ptD Dependent variable: GM volume		Region	Hemis-phere	Cluster Peak MNI - coordinates			Z-Score	Cluster size
				x	y	z	peak voxel	K = 1 mm^3
at baseline	positive association	**HOc1 (V1)**	**L**	**−27**	**−61**	**−2**	**4.39**	**627$^{(1)}$**
		HOc4v (V4)	L	−18	−78	−11	3.82	170
	negative association	**Postcentral gyrus (BA: 1,4a,3b)**	**L**	**−24**	**−39**	**69**	**- 4.49**	**178$^{(2)}$**
		Thalamus	**L**	**−20**	**−28**	**10**	**- 3.46**	**31$^{(2)}$**
		HOc5 (V5/MT)	R	53	−54	12	- 4.01	175
		IPL						
		IPL	R	44	−61	40	- 3.7	193
after rSS	positive association	Entorhinal cortex	R	21	2	−45	3.45	114
	negative association	**Postcentral gyrus (BA: 3a,3b,4a,4p)**	**L**	**−26**	**−34**	**63**	**- 3.74**	**191$^{(2)}$**

Abbreviations: BA = Brodmann area, GM = gray matter, HOc1 = primary visual cortex, IPL = inferior parietal lobule, L = left, MT = visual area MT5/V5, R = right. A negative association indicates that lower 2ptD thresholds, i.e. better performances predicted higher GM volume. Age was added as a covariate of no interest. Statistics: clusters are reported with a cluster size >50 contiguous voxels (p-value < 0.001 uncorrected). Of note, the cluster in the left thalamus did not pass this initial extent threshold. Correction for multiple comparisons: FWE correction on the cluster level ($p < 0.05$). $^{(1)}$ = corrected for multiple comparisons throughout the whole brain, $^{(2)}$ = corrected for multiple comparisons within a region of interest (left thalamus, left postcentral gyrus, left insula). Significant associations are highlighted in bold font. Anatomical labeling: regions were probabilistically determined using the Anatomy Toolbox by Eickhoff et al., 2005.

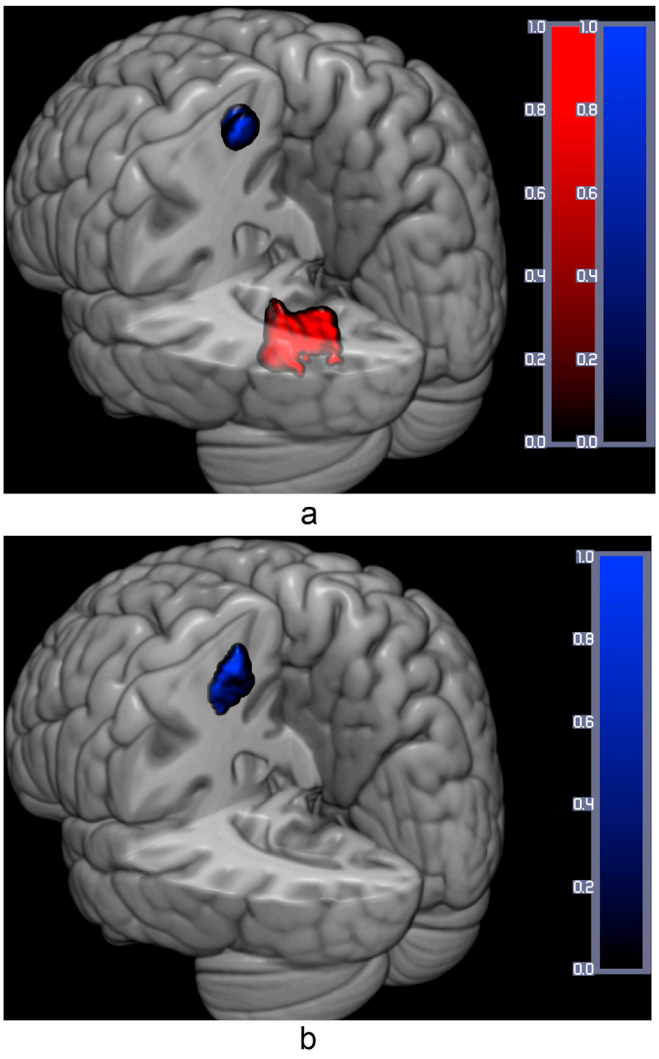

Fig. 3. (a) Association of the 2ptD of the dominant hand and the regional GM volume before rSS. Cluster in left visual cortex (red, peak-coordinate: x = −27, y = −61, z = −2, z-score: 4.39, cluster size: 627 voxels) is positively associated with the 2ptD threshold of the dominant hand. The cluster in postcentral gyrus (blue, peak-coordinate: x = −24, y = −39, z = 69, z-score: −4.49, cluster size: 178 voxels) is negatively associated with the 2ptD threshold of the dominant hand; i.e. the more the GM volume, the lower the threshold (and the higher the performance). (b) Association of the 2ptD thresholds of the dominant hand and the GM volume after rSS. The cluster in the postcentral gyrus (blue, peak-coordinate: x = −26, y = −34, z = 63, z-score: −3.74, cluster size: 191 voxels) is negatively associated with the 2ptD thresholds; i.e. the more GM volume, the lower the threshold (and the higher the performance).

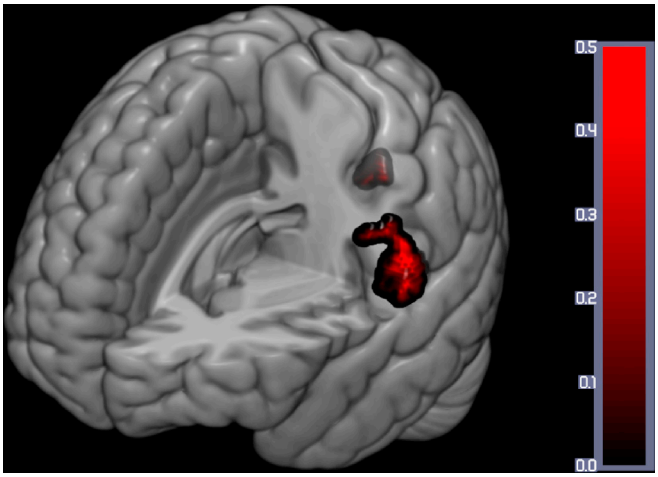

Fig. 4. Longitudinal analysis of the GM volume changes (pre < post). The GM volume of the clusters in the parietal operculum (red, peak-coordinate: x = -62, y = −12, z = 18, z-score: 4.67, cluster size: 301 voxel) and the cluster in the postcentral gyrus (red, peak-coordinate: x = −39, y = −33, z = 48, z-score 3.59, cluster size: 66 voxels) show an increase in GM after rSS of the right hand.

somatosensory cortex (OP4) and the amygdala (r = 0.49; p = 0.03), and a trend towards a positive correlation between the OP4 cluster and the cluster in the postcentral gyrus (primary somatosensory cortex; r = 0.4, p = 0.09; Table 4); i.e. study participants showing a strong increase in GM in the left OP4 also showed a strong increase in the left primary somatosensory cortex (trend) and a less pronounced decrease in the right amygdala.

Regression between change in performance and changes in gray matter

To further determine associations between changes in performance (Δ performance) and changes in regional GM volume (Δ GM), we

Table 4
Correlation matrix of gray matter changes. Significant correlations are highlighted in bold font.

Region		Hippocampus	Postcentral gyrus	Amygdala
OP4	r*	0.28	0.4	**0.49**
	p	0.24	0.09	**0.03**
Hippocampus	r*		−0.18	−0.029
	p		0.46	0.91
Postcentral gyrus	r*			0.31
	p			0.19

Abbreviations: BA = Brodmann area, OP = parietal operculum: * = adjusted. Correlation of GM differences (pre and post stimulation). GM values were extracted from a 10 mm sphere (from the normalized smoothed images) using MarsBaR, the sphere was centered around the peak-coordinate of the clusters identified by the longitudinal analysis.

Table 3
Changes in regional gray matter volume–longitudinal analysis.

Paired *t*-test	Region	Hemisphere	Cluster Peak MNI - coordinates			Z-Score	Cluster size
			X	y	z		K = 1 mm^3
pre < post	**OP4**	**L**	**−62**	**−12**	**18**	**4.67**	**301** [(2)]
	BA 3b						
	Hippocampus (CA1, CA2)	R	35	−34	−9	3.59	71
	Postcentral gyrus	L	−36	−28	40	3.59	66 [(3)]
	(BA: 2, 3a, 3b)						
pre > post	Amygdala	R	26	0	−26	−3.70	121

Abbreviations: BA = Brodmann area, OP = parietal operculum, L = left, R = right. Statistics: clusters are reported with a cluster size >50 contiguous voxels (p-value < 0.001 uncorrected). Correction for multiple comparisons: FWE correction on the cluster level (p < 0.05): [(1)] = corrected for multiple comparisons within a region of interest (left thalamus, left postcentral gyrus, left insula etc.). [(2)] = close projection to the representational field of the hand (Kim et al., 2014). Significant associations are highlighted in bold font. Anatomical labeling: regions were probabilistically determined using the Anatomy Toolbox by Eickhoff et al., 2005.

performed a regression analysis (between Δ performance and Δ GM). There was a trend towards a negative association in a cluster located in the left anterior IC ($p = 0.057$, after FWE correction within the left IC; peak coordinates: $x = -33$, $y = 14$, $z = -18$; $k = 82$ voxels; Table 5 and Fig. 5a), such that a gain in performance predicted a decrease in GM. For visualization purposes GM difference values were extracted from this cluster and plotted against 2ptD (r^2-adjusted = 0.55, $\beta = -0.84$, $p < 0.001$; Fig. 5b).

Discussion

In the current study, we sought to determine how properties of local brain structures relate to performance in a 2ptD task, and whether rSS, an intervention known to improve tactile perception, leads to changes in brain structure. We found that at baseline, performance in a 2ptD task was associated with regional GM volume in the left thalamus and the left SI. Behaviorally, rSS led to an improvement of 2ptD of the stimulated hand, whereas no improvement of tactile performance was seen on the non-stimulated side. Furthermore, rSS was associated with an increase in GM volume in the left operculum extending into the SII cortex. Additionally, an increase in GM was observed in the left postcentral gyrus, projecting to the anticipated representational field of the right hand, the right hippocampus and the right amygdala. Of note, the clusters in the left postcentral gyrus, the hippocampus and the amygdala did not survive corrections for multiple comparisons and should thus be viewed with caution. There were no associations between changes in GM volume and increase in tactile perception in these two regions. Finally, an association between ΔperformANCE and ΔGM was observed in the left anterior IC. To our knowledge, this is the first study that relates tactile performance (2ptD) to regional brain morphology and describes changes in regional brain morphology related to rSS.

There is a well-established body of literature examining the functional neuroanatomy of brain regions underlying 2ptD, with SI serving as the main sensory entry site and sequentially aligned upstream areas, such as the SII, the posterior parietal cortex, the supramarginal gyrus and the IC being involved in higher-level processing as well as multimodal integration (Kalberlah et al., 2013; Lucan et al., 2010; Makin et al., 2007; Preusser et al., 2015; Sathian, 2016; Stilla et al., 2007; Zhang et al., 2005). Lesions of the SI, for example, have been shown to affect the detection of tactile stimuli while lesions of the posterior parietal cortex are associated with impairments of more complex functions such as shape recognition. Using VBM, the current study focused on structural properties of the tactile system with the goal of relating tactile performance to regional brain morphology, with strong *a priori* hypotheses for the SI and SII.

The cluster showing an association between performance and GM volume (at baseline and after rSS) was located in the SI, but with respect to the current literature, the cluster was shifted toward the representational field of the shoulder. However, the representations of single fingers as delineated by functional imaging show some variations across the postcentral gyrus (Kim et al., 2014); furthermore, it may be possible that the border areas of representational fields account for interindividual differences in performance. Interestingly, Muret et al. recently demonstrated that improvement in tactile perception of the hand via rSS transfers to the face suggesting that border areas may play an important role in perception as well as learning and plasticity (Muret et al., 2014).

Surprisingly, we also found an association between regional GM volume within the left primary and secondary visual cortex. Lower GM volumes were associated with better performance in 2ptD at baseline. This association was not observed after rSS. The visual cortex was not part of our *a priori* hypotheses; however, the cluster survived correction for multiple comparisons in the explorative whole-brain analysis, making this finding worth discussing.

It has been demonstrated that the visual cortex is involved in tactile perception. Sathian et al. (1999) were the first to report that disrupting the function of the occipital cortex via transcranial magnetic stimulation interferes with tactile discrimination of grating orientation (Sathian et al., 1999). Furthermore, perception-related visual input can enhance tactile perception (Colino et al., 2016). For example, tactile acuity improves when a vision of the relevant body part is available (Eads et al., 2015; Schaefer et al., 2005) and it has been suggested that the posterior parietal cortex serves as a multimodal integration site. On the other hand, visual dominance over other senses is a well-known phenomenon and it has repeatedly been shown that closing one's eyes, even in the dark, can improve tactile performance, possibly by increasing functional connectivity between the thalamus and the somatosensory cortex (Brodoehl et al., 2015). With respect to GM volume, our results suggest opposing associations between baseline performance and GM volume in the two sensory cortices. Importantly, the tactile assessment was performed after scanning, thus, it is unlikely that the task itself induced variance in the GM volume. We hypothesize that within a unimodal setting tactile performance profits from a “weaker” and/or down-regulated visual system in strong tactile performers, given that lower GM volume indicates such a functional down-regulation. However, this is speculative and more work is needed to both reproduce this finding and to give more insights into the relationship between function and GM volume.

The clusters indicating changes in regional GM volume associated with rSS were located both in the parietal operculum reaching into the SII cortex and to the representational field of the right hand/fingers within the left SI cortex. For these two regions, we had strong *a priori* hypotheses, as they serve as sensory input channels to the cortex and after thalamic gating, and are likely to be directly influenced by the stimulation. Overall, our data suggest that rSS applied to the right hand has a direct and fast occurring impact upon regional GM volume within the left somatosensory system. Dynamic changes in gray and white matter related to learning have been described in quite a few studies investigating motor learning (Draganski et al., 2004; May et al., 2007), semantic learning (Schlaffke et al., 2017; Schmidt-Wilcke et al., 2010) and various kinds of perceptual learning (Ilg et al., 2008); for a review see Taubert et al. (2010). Improvement in tactile perception in the current study was induced via high-frequency stimulation (20 Hz) and co-activation. Furthermore, it was completely training-independent. Brain imaging studies have shown that these stimulation protocols can lead to an enlargement of the cortical representation specific to the co-activated fingers in SI and SII, and that the degree of individual enlargement in SI correlate with the individual decrease in 2ptD thresholds (Dinse et al.,

Table 5
Association between change of two-point discrimination thresholds (Δ pre-post) and change in regional gray matter volume.

Multiple regression Predictor variable: Δ 2ptD (2ptD dom, Δ pre-post) Dependent variable: Δ GM volume GM image (Δ post-pre)	Region	Hemis-phere	Cluster Peak MNI - coordinates			Z-Score	Cluster size
			x	y	z		K = 1 mm^3
negative association	Anterior Insula	L	−33	14	−18	- 3.62	82[(2)] Cluster level statistics: p = 0.057

Abbreviations: 2ptD = two-point discrimination, dom = dominant, GM = gray matter. Association between the change in 2ptD thresholds (Δ pre–post) of the stimulated hand and the change in GM (Δ post–pre); i.e. an increase in performance was associated with a decrease in GM volume in the left anterior insular. Difference images (Δ GM volume) were calculated using the ImCalc function implemented in SPM for the subtraction of the GM images. Correction for multiple comparisons: [(1)] = corrected for multiple comparisons within a region of interest (left insula). Regression analysis was performed with age as covariate of no interest. Regions were probabilistically determined using the Anatomy Toolbox by Eickhoff et al., 2005.

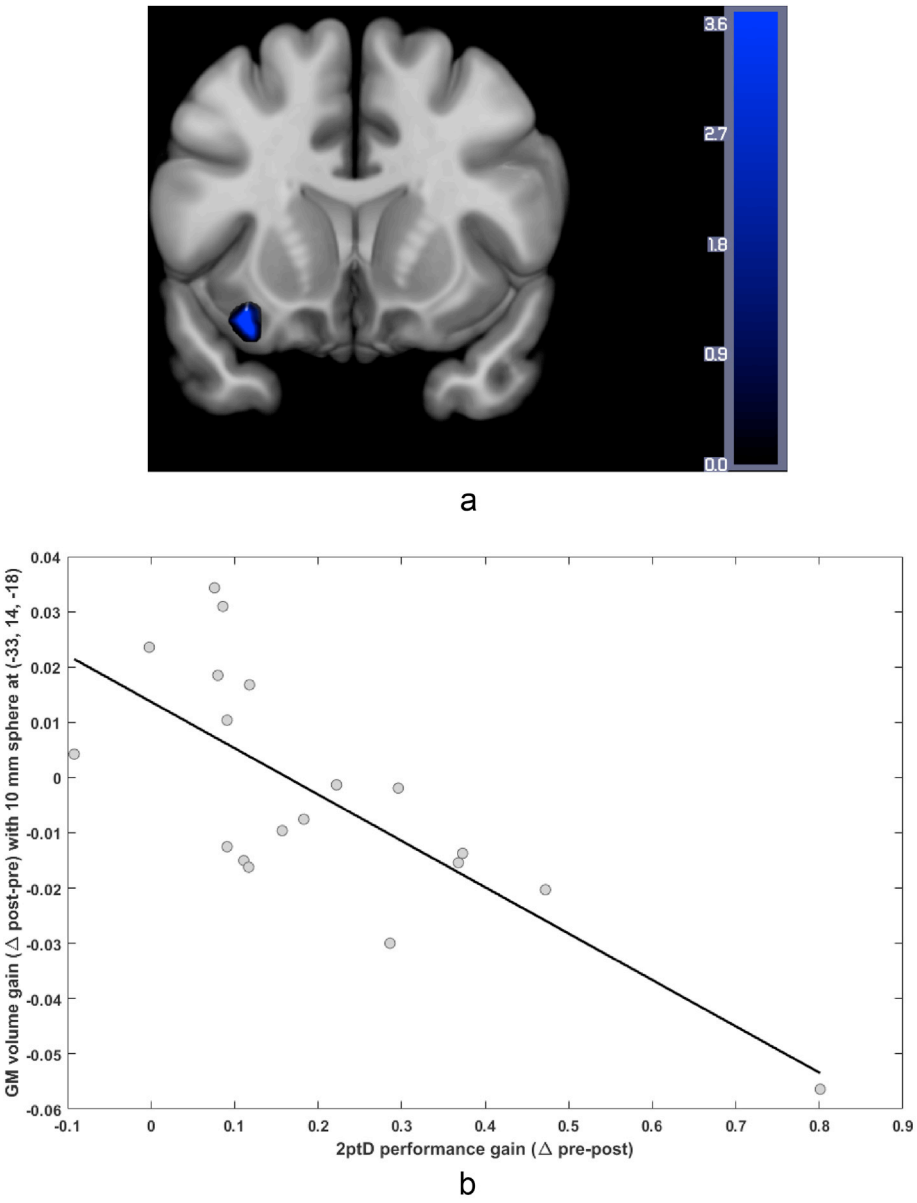

Fig. 5. (a) Association between the change in the 2ptD thresholds (Δ pre – post) of the stimulated hand and the change in GM (Δ post – pre); i.e. an increase in performance was associated with a decrease in GM volume in the left insular cluster (peak-coordinate: x = −33, y = 14, z = −18, z-score: 3.62, cluster size: 82 voxels). (b) Association between the change in two-point discrimination thresholds (x-axis) and the change of GM volume (y-axis); r^2-adjusted = 0.55, β = −0.84, p < 0.001), i.e. an increase in performance was associated with a decrease in GM volume. GM values were extracted from a 10 mm sphere (from the difference images) using MarsBaR. The sphere was centered around the peak-coordinate of the cluster identified in the whole brain regression analysis (peak-coordinates: x = −33, y = 14, z = −18).

2003; Pleger et al., 2003). Both the behavioral as well as the neural effects can be suppressed by the application of the NMDA receptor blocker *memantine* (Dinse et al., 2003). Against this background, it has been hypothesized that rSS works through a Hebbian-like mechanism inducing synaptic plasticity.

One drawback of VBM studies is that the neural/histological correlates of these changes are not clear. Spines, for example, can be built within minutes (Bosch et al., 2014; Trachtenberg et al., 2002; Xu et al., 2009), and given that they remain stable, new synapses can develop within an hour. However, synaptic plasticity and/or synaptogenesis alone would not be discernible on MR images of this resolution and other mechanisms like astrocyte swelling or changes in regional blood flow/volume need to be considered (Zatorre et al., 2013). Given that rSS leads to continuous neural activation in SI and SII during the stimulation, i.e. for 45 min, increased blood flow/volume extending 10–15 min beyond the actual stimulation period would be a strong candidate to account for some of the GM changes observed, especially since changes in GM in the current study were not related to changes in performance. Overall the changes in GM are likely to represent a conglomerate of cellular and extracellular mechanisms.

It is also worth discussing the speed of change. While changes in brain morphology as delineated by VBM and DTI have been described in the course of days to weeks (Ilg et al., 2008; May et al., 2007; Taubert et al., 2012), the observed changes in this study took place within 1 h. To our knowledge, these are the fastest changes in regional brain morphology reported so far. Sagi et al. reported microstructural changes in the medial temporal lobe as delineated by DTI taking place within 2 h, in participants undergoing a spatial learning task (Sagi et al., 2012). Although for both VBM and DTI the exact neurobiological underpinnings determining such changes remain to be fully elucidated, these results suggest a fast adaptation in the adult brain that possibly not only relates to the learning process *per se* but also supports consolidation via structural reorganization. It must also be noted that the observed structural changes in SI and SII did not correlate with the change in performance, nor did baseline GM

volume within the somatosensory cortex predict improvement after rSS. We speculate that the changes seen are based on a variety of mechanisms, both related and unrelated to cortical plasticity.

Additionally, we could identify one region in the left anterior IC where the change in GM volume is associated with the change in performance. The IC plays an important role in a variety of tasks, such as tactile perception (within the ventral processing stream) (Li Hegner et al., 2010), pain perception, multimodal integration (Coghill et al., 1994; Craig, 2011), etc. Specifically, the anterior IC has been hypothesized to coordinate the hierarchical processing of tactile prediction error (Allen et al., 2016), and might potentially be involved in decision-making. Our results suggest that the anterior IC determines to what degree individuals profit from rSS, although it might not be directly affected by the intervention. Interestingly, a gain in performance was associated with a decrease in GM volume, which implies that it is not always an increase in GM that is related to better performance. However, as with other brain regions, the underlying neural mechanisms remain to be fully elucidated.

There were two more interesting findings in our study, which are worth mentioning. Apart from the GM changes in the somatosensory system, we also observed an increase in GM volume in the right hippocampus and a decrease in the right amygdala. Both regions were not part of our *a priori* hypotheses, but are nevertheless interesting. The hippocampus is known to play an important role in both learning and multimodal integration (Adams et al., 1997); in animal studies, for example, the coherence between the somatosensory system and the hippocampus increases during the collection of sensory information and this possibly enhances the efficiency of integrating stimulus-specific information, into memory and decision-making (Grion et al., 2016). Notably, study participants in this study did not engage in an active memory task; however, it is conceivable that electrical stimulation (rSS), the initial assessment of 2ptD thresholds (repetitive stimulus presentation requiring a verbal rating), or a combination of both, elicited changes in the hippocampal GM.

The amygdala is known to play a critical role in the processing of aversive stimuli (Hamann et al., 1999). Although rSS is not painful, it can cause a feeling of discomfort during the first 5–10 min. Afterwards, study participants usually habituate and rSS is often not perceived consciously. Interestingly, in patients with sensory over-responsitivity, e.g. patients suffering from autism spectrum disorders, increased activity (and decreased neural habituation) in the somatosensory cortex and amygdala was found in response to mildly aversive tactile stimuli (Green et al., 2015). From a network perspective, the eigenvariates derived from the OP4 and amygdala clusters in the difference images were positively correlated in our study; i.e. the less the decrease in amygdala GM, the higher the increase in OP4 GM. VBM does not allow any assumptions on up – or down – regulations (with respect to activity and/or functionality), however, it is tempting to hypothesize that both systems interact with each other. Less pronounced changes in the amygdala (in terms of a decrease) are associated with more pronounced changes in the somatosensory system, which on a group level seems to benefit the learning process. Against this background, it could be very interesting to collect data on discomfort, to specifically investigate whether discomfort in this specific learning paradigm interacts with learning, and to investigate possible neural interactions, using connectivity analyses.

There are some limitations to our study that need to be addressed. Although VBM is very helpful in detecting macro-changes in regional brain morphology, the cytoarchitectural correlates remain to be fully elucidated. As such, the biological interpretation of changes detected by VBM remains challenging. Multimodal imaging, e.g. VBM, in combination with arterial spin labeling with the goal of detecting changes/differences in regional blood flow, will most likely help to further delineate effects of learning and practice on regional brain structure. Currently, VBM has also been successfully applied to animal models (Biedermann et al., 2012; Seminowicz et al., 2009), which potentially allows cross-validation between MRI findings and cytoarchitecture and holds promise to facilitate interpretation of macro-changes detected in humans (using VBM). Also, more information is required regarding the short-term dynamics of VBM changes. The intervention in our study lasted 45 min, the interscan interval however varied between 55 and 70 min. If the changes were entirely related to neural mechanisms like spine and synapse formation, we would think that these time differences are not that relevant. However, if some of the structural changes observed are related to blood flow, then these differences in interscan intervals may actually have a relevant impact; therefore, these intervals should be kept stringently constant in future studies. As the representational fields of single fingers vary between participants across the SI, it would also be important for future studies to localize these fields intra-individually using fMRI. This would allow more fine-grained analyses to be performed, possibly without the necessity of normalizing images which tends to spatially blur the statistical results. Finally, it needs to be pointed out that this study lacks a proper control group. The intervention's effect (increase in regional GM volume) was only seen in the SI and SII of the left hemisphere contralateral to the simulated hand. No such effects were observed on the right side, which would have allowed the argument that the non-stimulated side serves as a control condition. Thus, future studies should aim to include a control group that undergoes sham stimulation.

In summary, we report an association between tactile perception and regional GM volumes within the SI. We also describe detected changes in regional brain morphology following rSS within the SI and SII contralateral to the stimulated hand, which takes place within a short period of time (only 45 min). More work is needed in order to determine the neurobiological underpinnings and the short-term dynamics of these changes. Interestingly, structural changes were also observed outside the classical tactile system, such as in the hippocampus and the amygdala. These findings may be of interest to future studies aimed at integrating multiple brain sites into a conceptual framework of perception and developing a network perspective.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.neuroimage.2017.10.016.

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