Neuroanatomic Correlates of Female Sexual Dysfunction in Multiple Sclerosis

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Abstract

Objective: This study intended to determine associations between alterations of female sexual arousal as well as vaginal lubrication and the site of cerebral multiple sclerosis (MS) lesions.

Methods: In 44 women with MS (mean age 36.5±9.9 years), we assessed their medical history and evaluated sexual function using the Female Sexual Function Index scores for arousal and vaginal lubrication. We determined potential confounding factors of sexual dysfunction: age, disease duration, physical disability, depression, bladder or urinary dysfunction, and total volume of cerebral lesions. Arousal and lubrication scores were correlated with each other and with potential confounding factors. Cerebral MS lesions were recorded on imaging scans. A voxel-based lesion symptom mapping (VLSM) analysis adjusted for confounding variables was performed correlating cerebral sites of MS lesions with arousal and lubrication scores.

Results: Decreased arousal scores correlated with decreased lubrication scores; decreased lubrication scores were associated with bladder or urinary symptoms. Arousal and lubrication scores were not associated with any other variables. Multivariate VLSM analysis including arousal and lubrication scores as covariables of interest showed right occipital lesions associated with impaired arousal and left insular lesions associated with decreased lubrication. Impaired lubrication remained associated with left insular lesions after adjustment for bladder or urinary dysfunction.

Interpretation: Our data indicate that impaired female sexual arousal is associated with MS lesions in the occipital region integrating visual information and modulating attention towards visual input. Impaired lubrication correlated with lesions in the left insular region contributing to mapping and generating visceral arousal states.

Keywords: Multiple sclerosis, female sexual dysfunction, autonomic dysfunction, sexual arousal, vaginal lubrication, voxel-based lesion symptom mapping

Introduction

Multiple sclerosis (MS), a common neuro-inflammatory disease, is frequently associated with sexual dysfunction.[1-5] In women with MS, disorders of sexual arousal and vaginal lubrication, the somatic manifestation of the subjectively perceived sexual arousal, are particularly frequent complaints[1-5] and might be related to MS-specific brain lesions. In MS patients, magnetic resonance imaging (MRI) shows a predilection of cerebral changes in the periventricular white matter, juxtacortical U-fibers, cortical areas, but also in the brainstem and cerebellum.[6, 7]

According to animal studies, female sexual behaviour is activated in subcortical regions, such as the paraventricular nucleus, the medial preoptic area and ventromedial nucleus of the hypothalamus, the amygdala, midbrain, and nucleus accumbens.[8, 9] In healthy women, functional neuroimaging during sexual arousal shows increased neural activity in the prefrontal or orbitofrontal cortex, the occipitotemporal visual association areas and in regions with a prominent autonomic role, such as the insula, cingulate gyrus and hypothalamus.[10, 11]

So far, there are only few studies investigating associations between sexual dysfunction and MS-related cerebral changes. Two studies linked MS-related pontine atrophy to sexual dysfunction.[2, 12] Barak et al. described associations of anorgasmia with brainstem lesions or corticospinal tract lesions, and also with the total area of brain lesions.[5]

However, there are no studies assessing the association between specific lesion sites and altered sexual arousal or vaginal lubrication in women with MS. We hypothesize that MS lesions located in brain areas that contribute to sexual function in functional neuroimaging studies may alter female sexual arousal and lubrication. In this study, we therefore assessed the cerebral and spinal cord MS lesion load on MRI scans in women with MS and determined parameters of female sexual arousal and lubrication as well as potential confounding variables

of sexual dysfunction. We correlated parameters of female sexual arousal and lubrication with the site of MS-related MRI changes using voxel-based lesion symptom mapping (VLSM).

Patients and methods

Patients

This study was conducted between February 2011 and February 2012 at the University Hospital Erlangen of the Friedrich-Alexander-University Erlangen-Nürnberg. We studied women with MS who fulfilled the following inclusion criteria: i) women with relapsing-remitting or secondary progressive MS, ii) aged 18 to 65 years, and iii) participation in sexual activity. Diagnosis of relapsing–remitting MS was defined according to the revised McDonald criteria of 2010.[13] We excluded patients with i) evidence of structural cerebral diseases other than MS, ii) patients with diseases interfering with autonomic nervous system function such as diabetes mellitus, and iii) patients taking substances that modify sexual behavior. The study has been approved by the local institutional ethics committee of the Friedrich-Alexander University Erlangen-Nürnberg. Prior to the study, all women gave written informed consent according to the Declaration of Helsinki.

In all women, we took the medical history with particular emphasis on disease course, co-morbidities and medication, and performed a physical examination. We determined the degree of physical disability using the Expanded Disability Status Scale (EDSS) scores.[14] We rated depression using the abridged Beck's depression Index (BDI), a 20-item questionnaire, with ratings from 0 to 5 per item and a maximum score of 100.[15] An overall BDI score above 35 indicates with a certainty of 90% that the patient has clinical manifest depression.[15] Because bladder and urinary symptoms are frequently associated with sexual dysfunction,[4, 12, 16] we determined severity of bladder or urinary symptoms using scores of item 2 of the 19-item

Multiple Sclerosis Intimacy and Sexuality Questionnaire (MSISQ-19).[17] The item 2 scores bladder or urinary symptoms over the last 6 months with ratings from 1 (never) to 5 (always).[17]

Assessment of female sexual arousal and lubrication

In all patients, we evaluated the subjectively perceived sexual arousal and vaginal lubrication using the specific arousal and lubrication scores of the validated Female Sexual Function Index (FSFI).[18] The four items of the specific FSFI score for arousal evaluate frequency, level, confidence, and satisfaction of sexual arousability in the last 4 weeks prior to examination with a possible score of 0 to 5 per item.[18] A score of 0 indicates no sexual activity. As mentioned above, these patients had to be excluded from the lesion-symptom analysis. For each of the four sexual arousal items, a score of 5 indicates that the patient is almost always sexually aroused during sexual activity, has a very high level of sexual arousability, is very confident to become sexually aroused during sexual activity, and is almost always satisfied with sexual arousability.[18] The four FSFI items assessing lubrication evaluate the frequency and difficulty of initiating vaginal lubrication during sexual activity or intercourse as well as the frequency and difficulty to maintain lubrication until the end of sexual intercourse in the last 4 weeks prior to examination. Again, the four items are scored from 0 to 5.[18] For each of the four lubrication items a maximum score of 5 indicates that the patient becomes almost always lubricated during sexual activity, has no difficulty becoming lubricated during sexual activity or intercourse, is almost always able to maintain vaginal lubrication until the end of sexual intercourse and has no difficulty maintaining lubrication until completion of sexual activity or sexual intercourse.[18] The sum score of the items for sexual arousal or vaginal lubrication is multiplied by 0.3; thus, FSFI scores for arousal or lubrication range from a minimum of 0 to a maximum of 6.[18]

Imaging

All women underwent 1.5T or 3T MRI of the brain and spinal cord. MRI scans of the brain included axial or 3D fluid-attenuated recovery (FLAIR) sequences for detecting cortically located or supratentorial MS lesions and axial T2 weighted images for detection of the infratentorial MS lesion load. Furthermore, sagittal FLAIR or T2 weighted MRI scans were performed for analyzing MS lesions in the callosal radiation or corpus callosum. Spinal cord lesions were analyzed on sagittal and axial T2 weighted MRI scans.

Voxel-based lesion symptom mapping

Two experienced investigators (K.W. and F.S.) manually delineated the boundaries of the MS lesions in the brain on anonymized axial T2 weighted MRI scans using MRIcron (www.mrico.com).[19] Lesion location was controlled for consistency on axial FLAIR or 3D FLAIR scans but delineated only on axial T2 weighted MRI scans. To ensure that no perivascular spaces were scored as MS lesions, lesions were only delineated if they were detectable on T2 as well as on FLAIR scans as a hyperintense lesion. To avoid observer bias both raters were blinded to clinical parameters during imaging analysis. The MRI scan and the lesion shape were transferred into stereotaxic space using the normalization algorithm of SPM8 (Wellcome Department of Cognitive Neuroscience, University College London, UK; http://www.fil.ion.ucl.ac.uk) and the Clinical Toolbox for SPM8 (http://www.mricro.com/clinical-toolbox/spm8-scripts).[20] Using the MR-segment-normalize algorithm of the Clinical Toolbox, the MR images were transformed to the T1 template.[20] To determine associations between MS lesion location and alterations of female sexual arousal and lubrication, continuous FSFI-scores for arousal and lubrication were correlated voxel-wise with lesion location using t-test statistics.[19] For these univariate analyses two

independent tests were performed, one for arousal and one for lubrication scores and a false discovery rate (FDR) correction of q <0.01 was applied to correct for multiple comparisons. Only voxels that showed lesions in at least three individuals were included in the analysis. VLSM analysis was adjusted for confounding factors identified in the univariate correlation analysis using multivariate logistic regression analyses. For the first multivariate logistic regression analysis, the binary dependent variable was whether a voxel was lesioned or not and scores for arousal and lubrication were the independent covariables of interest. In a second multivariate logistic regression analysis voxel-wise correlations between lubrication scores and cerebral sites of lesioned voxels were normalized for bladder or urinary symptoms. For voxel-wise multivariate logistic regression analyses, we applied a FDR correction of q <0.05. Lesion volumes were calculated using non-parametric mapping (NPM) software implemented in the MRIcron software package. To determine damaged brain regions, affected voxels were overlaid on the Automated Anatomical Labeling (AAL) atlas.[21] The peak coordinates of the involved regions are presented in Montreal Neurological Institute (MNI) space.

Statistical analysis

For data analysis, we used a commercially available statistical program (SPSS 20.0; IBM, Armonk, NY). To test data for distribution, we used the Shapiro-Wilk test. Data are presented as median and interquartile ranges (IQR). Arousal and lubrication scores were correlated with age, disease duration, EDSS scores, BDI scores, MSISQ-2 scores, and total volume of MS lesions throughout the brain using the Spearman rank correlation coefficient. Arousal scores were correlated with lubrication scores using Spearman rank correlations. Arousal and lubrication scores were compared between patients with depression and no depression using the Mann-Whitney U-test. Arousal and lubrication scores were compared between patients

with evidence of cervical, thoracic or multiple spinal cord lesions and those who did not have spinal cord lesions using the Kruskal-Wallis test. The level of statistical significance was set at $p < 0.05$.

Results

Patient characteristics

Of 58 women with MS screened, 44 patients fulfilled the inclusion criteria and were eligible to be included in the lesion-symptom analysis. Table 1 summarizes clinical and imaging data as well as correlation coefficients between clinical data and scores for arousal and lubrication. FSFI scores for arousal ranged from 1.2 to 6 (median, 5.1; lower quartile, 4.2; upper quartile, 5.7). FSFI scores for lubrication ranged from 1 to 6 (median, 5.7; lower quartile, 4.7; upper quartile, 6). At the time of examination, a total of nine women had no disease modifying therapy, 17 women were on natalizumab therapy, seven had interferon or glatiramer acetate treatment, six patients received oral therapies (i.e. azathiporine, dimethyl fumarate, fingolimod, or teriflunomide), three women received experimental therapy with monoclonal antibodies and two had mitoxantrone.

Correlation of sexual arousal and lubrication parameters

FSFI scores for arousal correlated with FSFI scores for lubrication (Spearman Rho, 0.55; $p < 0.001$). Arousal scores and lubrication scores did not correlate with patient age, disease duration, BDI scores, EDSS scores and total volume of cerebral MS lesions (Spearman rank correlation; $p > 0.05$). Lubrication scores but not arousal scores correlated inversely with MSISQ-2 scores. A total of 15 patients (34.1%) had depression (BDI score >35). Arousal and

lubrication scores did not differ between patients with depression and patients without depression (Mann Whitney U Test, $p > 0.05$).

Imaging characteristics

Figure 1 shows the overlap and distribution of T2 hyperintense MS lesions of all patients. The highest lesion overlap, i.e. highest prevalence of individuals with lesions in a given voxel, was seen in the periventricular region, especially the parietal white matter, both insular and subinsular regions, the bilateral callosal radiation, and the periaqueductal midbrain gray. A total of 11 patients (25.0%) had no evidence of MS lesions in the spinal cord, 18 patients (40.9%) had lesions in the cervical spinal cord only, five patients (11.4%) had MS lesions in the thoracic spinal cord, and 10 patients (22.7%) had multiple spinal cord lesions. Arousal and lubrication scores did not differ between patients without spinal cord involvement, and patients with cervical, thoracic or multiple spinal cord MS lesions (Kruskal-Wallis test, $p > 0.05$).

Voxel-based lesion symptom mapping

Figure 2A illustrates lesioned areas that were associated with decreased arousal scores. A total of 2051 lesioned voxels correlated with decreasing arousal scores, 1966 lesioned voxels were located in the gray matter and 85 voxels in the white matter. Associations between damaged voxels and arousal scores with corresponding voxel counts and peak coordinates in MNI space are demonstrated in Table 2. Decreasing arousal scores correlated with larger clusters of lesioned voxels most prominently in the right and left occipital cortex and right and left parahippocampal areas. Smaller clusters of lesioned voxels (<50 voxels) correlated in the

right gyrus rectus, right insula, left and right hippocampus, left amygdala, right cuneus, right precuneus, right caudate, left putamen, and right temporal pole.

Associations between lesioned voxels and decreasing lubrication scores with corresponding voxel counts and peak coordinates in the MNI space are shown in Table 3. A total of 3840 lesioned voxels correlated with decreasing lubrication scores, 2148 lesioned voxels were located in the gray matter and 1692 in the white matter. Decreasing lubrication scores correlated with a large cluster of lesioned voxels in the left insular cortex extending into the subinsular white matter tracts, putamen, left hippocampus, as well as left superior temporal gyral area (Fig 2B). Smaller clusters of lesioned voxels (<50 voxels) correlated in the left gyrus rectus, right and left parahippocampal areas, right amygdala, left and right calcarine areas, left cuneus, right lingual, left and right superior occipital gyral areas, left and right fusiform gyrus, right precuneus, right putamen, right superior temporal gyrus, and right middle temporal gyrus.

The first multivariate logistic regression analysis including both arousal and lubrication scores as regressors showed that only lesions in the right occipital (calcarine and lingual) areas were associated with decreased arousal scores (Fig 3A), and that lesions in the left insular juxtacortical region remained associated with decreased lubrication scores (Fig 3B). The second logistic regression analysis that was adjusted for bladder and urinary MSISQ-2 scores showed associations between decreasing lubrication scores and left insular lesions (Fig 3C).

Discussion

Sexual dysfunction is common among women with MS and seems to be associated with the site of cerebral MS lesions. In our 44 women with MS, voxel-wise analysis demonstrated correlations between dysfunction scores of arousal and lubrication and T2 hyperintense

lesions in two distinct cerebral networks. Impaired arousability correlated most prominently with lesions in the visual areas and less prominently with lesions of the right and left parahippocampal gyrus. Compromised lubrication correlated closely with a large lesion cluster in the left insular region, adjacent juxtacortical white matter and smaller lesion sites in the occipital cortex and left hippocampus.

Previous studies used region of interest analyses to assess associations between MS-related cerebral lesions and sexual dysfunction and showed discrepant findings.[2, 5, 12, 22] In male and female MS patients, previous investigators determined the MS lesion load in the whole brain, the frontal cortex, and the pons.[2, 12] Zorzon et al. found no association between sexual dysfunction and MS lesions in these three regions of interest.[12] Zivadinov and coworkers showed similar results in their univariate analysis but identified associations between pontine MS lesions and sexual dysfunction when using a multivariate analysis.[2] In 32 female and 9 male MS patients, Barak et al. reported that anorgasmia correlated with the total volume of MS lesions throughout the brain and more specifically with MS lesions in the brainstem and corticospinal tract.[5] In a specific region of interest analysis of MS lesions in 50 women, we recently showed associations between inhibited orgasmic function and T2 hyperintense lesions in the right occipital lobe and left temporal white matter but also found associations between disinhibited orgasmic function and MS lesions in frontotemporal and midbrain areas.[22]

Voxel-wise analysis provides more precise correlation with sexual dysfunction

In the present study, we determined voxel-wise lesions, then assessed the voxel-specific lesion overlap in our entire sample of MS patients, and performed univariate analyses between voxel-wise lesion overlap and dysfunction scores of arousal and lubrication. Finally,

multivariate analysis discriminated associations between voxel-wise lesion overlap and impaired arousal or lubrication into arousal-specific or lubrication-specific associations. Moreover, we considered confounding factors possibly compromising sexual function, such as depression, age, disease severity and duration, bladder dysfunction and total volume of cerebral MS lesions,[2, 4, 5, 12, 16] but only found a correlation between impaired lubrication and bladder dysfunction.

After further correction of the voxel-wise lesion analysis for bladder dysfunction in a multivariate logistic regression model, lesions in the left insular juxtacortical region remained associated with decreased lubrication. In contrast, impaired arousability was not associated with any of the above confounders but only correlated with decreased lubrication.

Impairment of arousability and lubrication depend on the site of MS lesions

While many previous studies indicate correlations between sexual dysfunction and patient age, MS duration and severity, depression, or spinal cord involvement,[2, 4, 5, 12, 16] our analyses show that dysfunction of arousal and lubrication may evolve in women with MS independently of these parameters. Only the study by Barak et al. also showed that sexual dysfunction does not necessarily depend on MS duration and severity but may occur even at early disease stages or with minor physical disability.[5] Our multivariate analysis confirms that impairment of arousability and lubrication does not primarily depend on the overall MS severity or duration but is due to MS lesions in strategic areas that are important modulators of female sexual function. This assumption is also supported by the lack of correlation between the total volume of cerebral MS lesions and changes of female sexual arousal and lubrication.

Lesion sites associated with impaired arousal

This rather specific approach towards identifying associations between circumscribed cerebral lesions and impairment of arousal and lubrication showed that female sexual arousal deteriorated with T2 hyperintense lesions in the right and left occipital and parahippocampal areas and in the multivariate voxel-wise analysis regressing out lubrication scores with lesions restricted only to right occipital lobe areas. According to Redouté and coworkers, the perceived sexual arousal is influenced by motivational, cognitive, emotional and autonomic factors.[23] In our sample, MS lesions located in the occipital visual areas inhibited female sexual arousal responses, probably by disrupting the motivational and attention components associated with sexual arousal.[10] The contribution of visual processing areas to sexual arousal was shown in several functional neuroimaging studies in healthy individuals exposed to visual sexual stimuli.[10, 11, 24] Emotionally arousing visual stimuli, such as visual sexual stimuli showed higher activation in occipital areas than did non-emotionally arousing or non-erotic stimuli such as geometric figures.[10, 11, 24] According to Karama et al., emotional stimulus-related enhanced activity in the visual cortex reflects increased subjective attention levels in individuals exposed to emotional stimuli.[10] Supporting this assumption, evidence from functional neuroimaging showed that attention to moving visual signals can modulate activity in a neural network consisting of primary visual, visual association areas as well as frontoparietal brain areas.[25] Based on these findings, the decrease in sexual arousability in women with lesions in the occipital areas might be related to disturbed processing and focusing attention to visual sexual stimuli, thereby compromising the subjectively perceived sexual arousal.

Lesion sites associated with decreased lubrication

While associations between impaired arousability and MS lesions were primarily limited to the right occipital lobe, impaired lubrication was associated with a more wide-spread and larger cluster of lesioned voxels including the left insula, adjacent juxtacortical white matter, left hippocampus and left putamen in the univariate analysis. However, in the multivariate voxel-wise analysis regressing out bladder or urinary dysfunction scores and arousal scores a smaller cluster of lesioned voxels in the left insular region remained associated with decreased lubrication. The insular cortex significantly contributes to generating and mapping visceral autonomic arousal states.[26-28] Bodily changes associated with sexual arousal are primarily mediated by parasympathetic activation and sympathetic inhibition, and include increased pelvic blood flow, labial engorgement, increased vaginal blood flow with arterial dilatation and enhanced vaginal lubrication.[29, 30] Based on our results, we hypothesize that there is a hemispheric predominance with the left insula mediating lubrication more prominently than the right insula. Several studies using hemispheric inactivation or insular stimulation showed hemispheric predominance of sympathetic and parasympathetic cardiovascular modulation, with more prominent sympathetic influence arising from the right and more parasympathetic activity arising from the left hemisphere.[31-35] Functional neuroimaging studies in healthy individuals confirmed the hemispheric lateralization of autonomic arousal.[36-42] In animals, insular cortex lesioning induced profound autonomic imbalance; depending on the side or site of the insular cortex lesions, there was increased sympathetic outflow, baroreflex impairment or decreased parasympathetic cardiovascular control.[35, 43] In ischemic stroke patients, Oppenheimer et al. showed that left insular cortex lesions were associated with an increase in cardiac sympathetic tone.[44] Similarly, left insular lesions in our MS patients may account for autonomic imbalance with enhanced sympathetic and decreased parasympathetic modulation which in turn compromises vaginal lubrication.[30, 45] Although frequently overlooked, autonomic dysfunction is common among MS patients.[46-49]

Limitations

There are several limitations to our study. Although VLSM provides rather precise data concerning associations between the location of cerebral lesions and sexual dysfunction, correlations do not necessarily allow drawing causal conclusions. Moreover, the technique only supports conclusions regarding associations between sexual dysfunction and sites of MS lesions for those brain areas that are compromised in a high enough number of MS patients. The evaluation of voxel-wise overlap of MS lesions fails to assess the sexual effects of lesions in brain regions that are rarely involved in the MS pathology. Thus, associations between altered arousability or lubrication and lesions in areas that are known to contribute to autonomic and emotional processing such as the prefrontal or orbitofrontal cortices, the hypothalamus, the cingulate gyrus or infratentorial areas cannot be adequately determined by the VLSM approach unless the sample size is far bigger than in our study.[50] Yet, our strict exclusion criteria ruling out the evaluation of patients with other possible causes of autonomic or sexual dysfunction, limited the number of patients suited for this study.

Moreover, autonomic dysfunction may vary significantly among MS patients.[46-49] In a different group of MS patients, autonomic sexual dysfunction might, therefore, correlate with somewhat different sites of cerebral MS lesions. Another limitation of our study is the fact that clinical data was obtained using questionnaires rather than more objective measures such as neurophysiologic methods.[30] However, in our clinical setting, we could not assess sexual function, particularly arousal and vaginal lubrication of our MS patients. Most of our patients would not have accepted a physical examination of sexual function, for example by means of quantitative sensory testing in the genital area or vaginal photoplethysmography.[30] Moreover, we were not prepared to induce sexual arousal or lubrication. We, therefore, had to rely on standardized and validated questionnaires.[14, 15, 17, 18]

Impact of sexual dysfunction in women with MS or other neurological conditions

So far, the impact of isolated central lesions on specific components of sexual function has not been sufficiently addressed in MS patients although sexual dysfunction is frequent among MS patients and may compromise their quality of life, self-esteem, family planning, and partnership.[1-5, 16, 30] While sexual dysfunction should be addressed in general during patient examination, women with lesions in the left insula or right occipital cortex must be informed about possible changes in their arousability and lubrication. Therapeutic advice and adequate awareness of the dysfunction may limit psychological sequelae and help ameliorate the physical limitation.[30, 45] While circumscribed lesions are rather typical in MS patients, similar lesions may occur after lacunar as well as more wide-spread strokes and in diffuse, e.g. neurodegenerative cerebral diseases including the above areas. Again, the risk of sexual dysfunction should be considered in patients with such lesions, and further studies should assess the relation between sexual function and cerebral lesions in patients with such diseases.

Conclusion

In conclusion, our VLSM data suggest that MS lesions in the occipital cortex compromise female sexual arousability while left insular cortex lesions impair vaginal lubrication. Surprisingly, in our MS patients dysfunction of sexual arousability or lubrication was not associated with the patient age, disease duration or severity, spinal cord involvement or depression.

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Author contributions

Conception and design of the study: K.W., F.S., M.J.H. Acquisition and analysis of data: K.W., F.S., M.D., T.E., A.D., D.L., K.M.H. Drafting a significant portion of the manuscript or figures: K.W., R.A.L., M.J.H.

Potential Conflicts of Interest

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Figure legends

Figure 1. Overlap and distribution of T2 hyperintense lesions of all patients thresholded to include only voxels which were lesioned in at least three patients. The number of overlapping lesions is illustrated by different colors coding increasing frequencies from dark red to yellow. Regions with higher lesion overlap counts are found symmetrically in periventricular regions, most prominently in the parietal periventricular white matter, as well as in the subinsular regions, and periaqueductal midbrain gray. Montreal Neurological Institute (MNI) z coordinates of each transverse section are given. L = left hemisphere; N = number of individuals; R = right hemisphere

Figure 2. Results of the univariate voxel-based lesion symptom mapping analyses.

Lesioned voxels in the occipital areas on both sides and in the parahippocampal regions were associated with decreased arousal scores (A). Decreased lubrication scores correlated most prominently with lesioned areas in the left insula, adjacent white matter tracts, putamen and left hippocampus (B). T-test statistics were conducted to assess correlations between lesion sites and continuous arousal and lubrication scores. Only voxels that were damaged in at least three individuals were included in the analysis. A false discovery rate (FDR) correction of $q < 0.01$ was applied. L = left hemisphere; R = right hemisphere; z = z-score

Figure 3. Results of the multivariate logistic regression analyses.

Decreased arousal scores remained associated with MS lesions only in the right occipital cortex after regressing out lubrication scores (A). A small cluster of lesioned voxels most prominently in the left posterior insular region was associated with decreased lubrication

scores after adjustment for arousal scores (B). Left insular lesions remained associated with decreased lubrication scores after regressing out urinary or bladder symptoms (C). A false discovery rate (FDR) correction of q <0.05 was applied. L = left hemisphere; R = right hemisphere; z = z-score

Table legends

Table 1. Demographic, clinical as well as sexual arousal and lubrication data.

BDI = Beck Depression Index; EDSS = Expanded Disability Status Scale; IQR = interquartile range; MSISQ-2 = item 2 of the Multiple Sclerosis Intimacy and Sexuality Questionnaire evaluating evidence of bladder or urinary symptoms; P = statistical significance

*indicates statistically significant correlation

Table 2. Result of the univariate voxel-based lesion symptom mapping analysis for arousal scores.

To determine associations between decreasing arousal scores and lesioned voxels t-test statistics were conducted. The corresponding voxel counts and peak coordinates outlined in Montreal Neurological Institute space are shown. Only areas that were afflicted by at least 50 lesioned voxels are reported.

Table 3. Result of the univariate voxel-based lesion symptom mapping analysis for lubrication scores.

To determine associations between decreasing lubrication scores and lesioned voxels t-test statistics were conducted. The corresponding voxel counts and peak coordinates outlined in

Montreal Neurological Institute space are shown. Only areas that were afflicted by at least 50 lesioned voxels are reported.

left temporal sup = left superior temporal gyrus

Figure 1

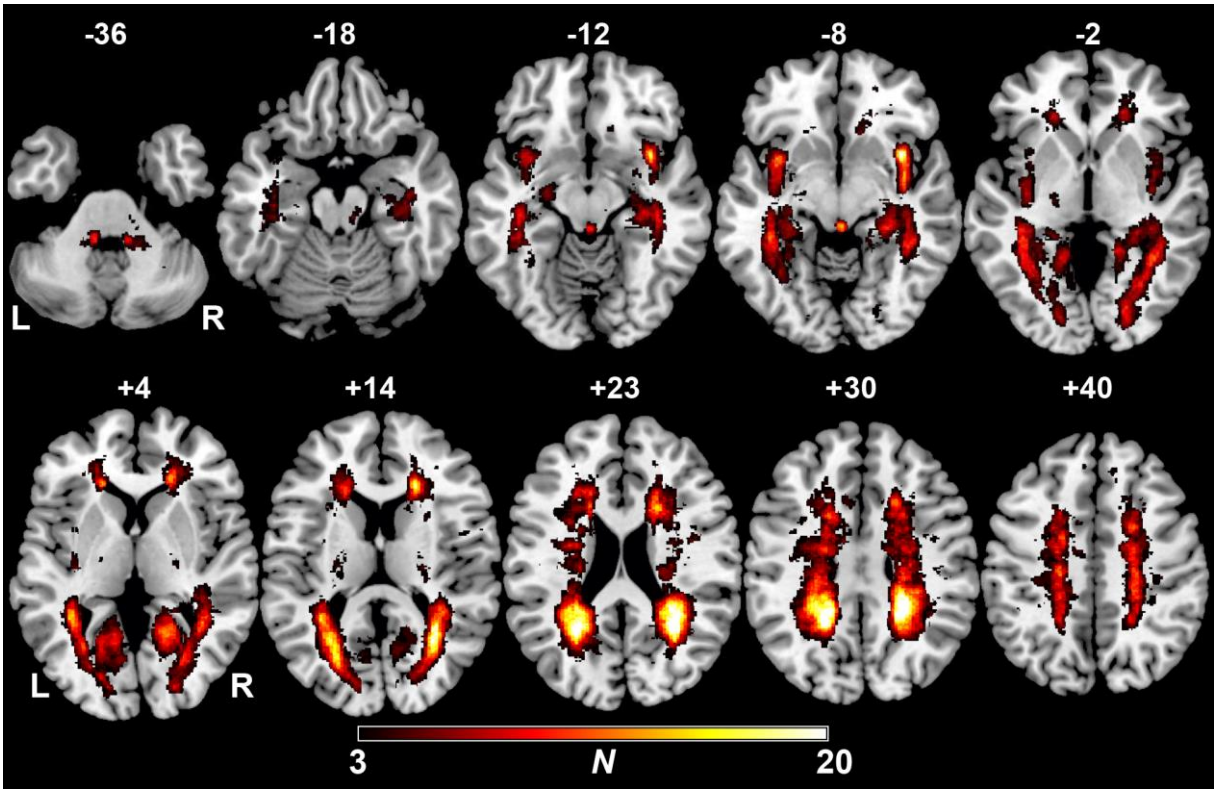

Figure 2

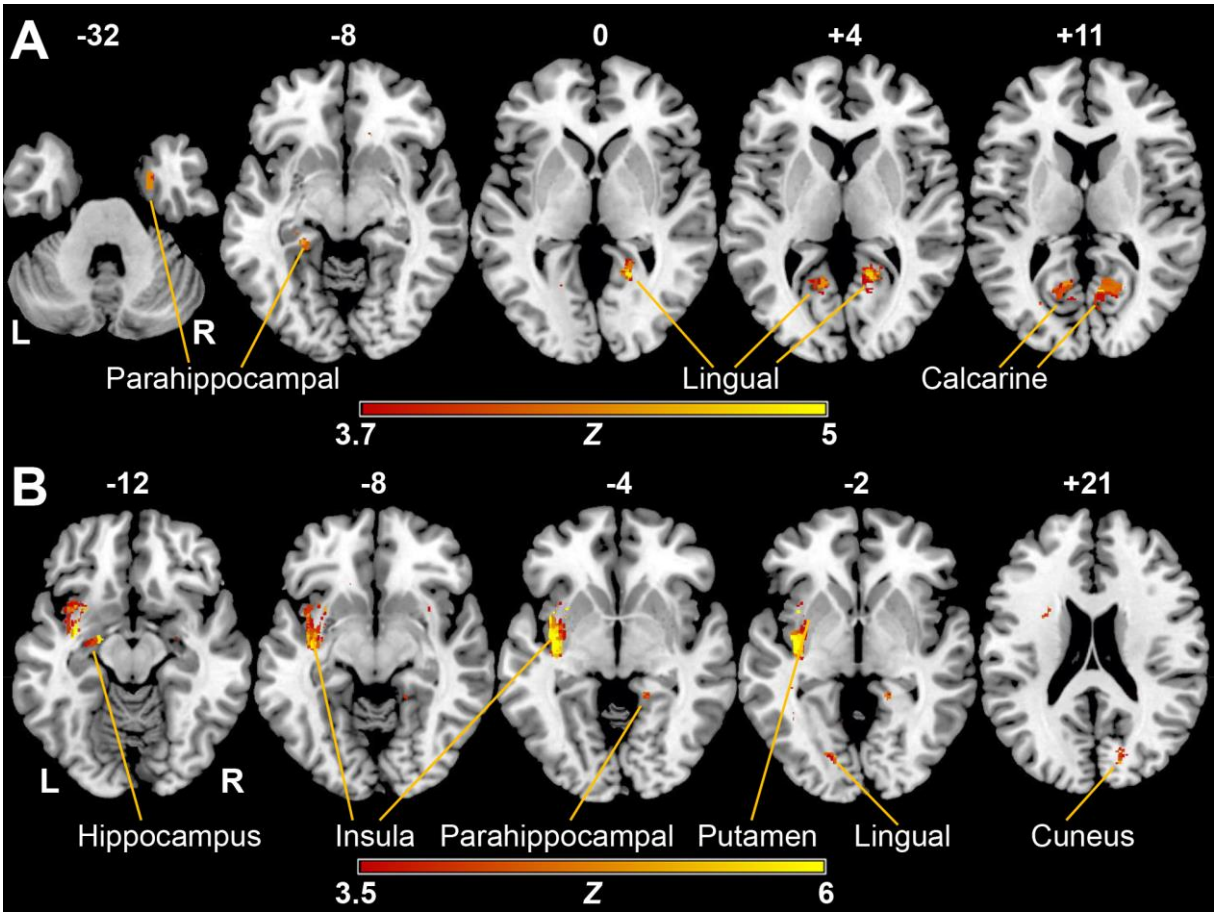

Figure 3

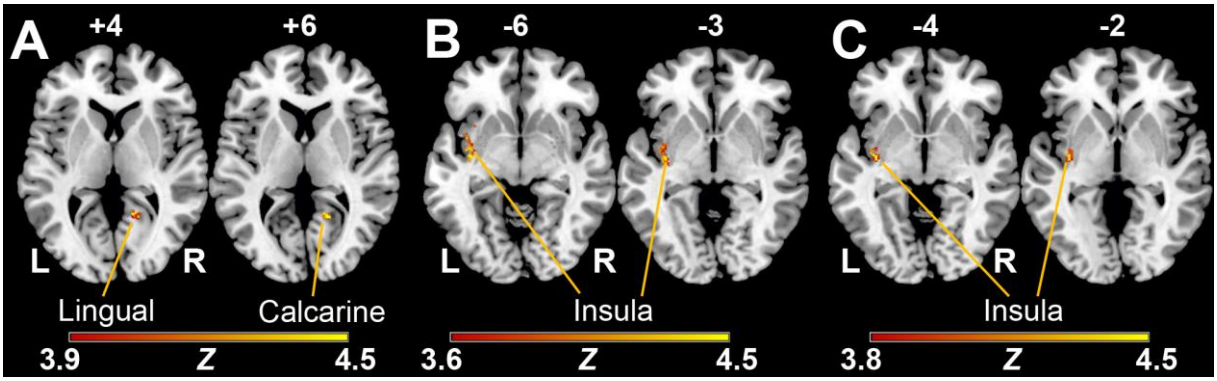

Table 1. Demographic, clinical as well as sexual arousal and lubrication data.

			Correlation with arousal scores		Correlation with lubrication scores	
Variable	Median	IQR	Rho	*P*	Rho	*P*
Patient age (yr)	36.0	28.7-42.5	-0.06	0.68	-0.04	0.79
Disease duration (months)	66.5	22.5-131.3	-0.07	0.65	-0.02	0.91
EDSS score	3.5	2-6	0.01	0.96	-0.06	0.72
BDI score	23	14-41.5	-0.26	0.09	-0.16	0.30
MSISQ-2 score	1	1-3	-0.17	0.27	-0.44*	0.003*
Total volume of lesions (ml)	25.2	13.9-38.6	-0.19	0.21	-0.08	0.61

BDI = Beck Depression Index; EDSS = Expanded Disability Status Scale; IQR = interquartile range; MSISQ-2 = item 2 of the Multiple Sclerosis Intimacy and Sexuality Questionnaire evaluating evidence of bladder or urinary symptoms; P = statistical significance

*indicates statistically significant correlation

Table 2. Result of the univariate voxel-based lesion symptom mapping analysis for arousal scores.

Lesion site	Voxels	*x*	*y*	*z*
Left parahippocampal	62	-24	-35	-9
Right parahippocampal	139	23	3	-34
Left calcarine	516	-13	-60	10
Right calcarine	570	8	-63	11
Left lingual	127	-12	-56	4
Right lingual	490	15	-55	4

To determine associations between decreasing arousal scores and lesioned voxels t-test statistics were conducted. The corresponding voxel counts and peak coordinates outlined in Montreal Neurological Institute space are shown. Only clusters consisting of at least 50 lesioned voxels are shown.

Table 3. Result of the univariate voxel-based lesion symptom mapping analysis for lubrication scores.

Lesion site	Voxels	*x*	*y*	*z*
Left insula	1167	-39	-9	-3
Left hippocampus	154	-20	-10	-12
Right cuneus	68	17	-81	21
Left lingual	99	-14	-78	-2
Left putamen	242	-30	10	-5
Left temporal sup	105	-41	-6	-6

To determine associations between decreasing lubrication scores and lesioned voxels t-test statistics were conducted. The corresponding voxel counts and peak coordinates outlined in Montreal Neurological Institute space are shown. Only areas that were afflicted by at least 50 lesioned voxels are reported.

left temporal sup = left superior temporal gyrus