Aus dem Institut für Medizinische Psychologie
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DISSERTATION

Experience-Related Structural Variation of the Human Female Somatosensory Genital Representation Field

Erfahrungsbezogene Strukturelle Veränderungen des Menschlichen Somatosensorischen Genitalen Repräsentationsfeldes bei Frauen

zur Erlangung des akademischen Grades
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AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
BA	Brodmann Area
BDNF	Brain-Derived Neurotrophic Factor
CAT	Computational Anatomy Toolbox
CEA	Childhood emotional abuse
CM	Childhood maltreatment
CNS	Central Nervous System
CPA	Childhood physical abuse
CS	Central surface
CSA	Childhood sexual abuse
CSF	Cerebrospinal fluid
CT	Cortical Thickness
DTI	Diffusion tensor imaging
EPI	Echoplanar image
fMRI	Functional magnetic resonance imaging
FWE	Family-wise error
HRF	Hemodynamic response function
GLM	General linear model
GM	Grey matter
GMV	Grey matter volume
LTD	Long-term depression
LTP	Long-term potentiation
MNI	Montreal Neurological Institute
MPRAGE	Magnetization-prepared rapid gradient echo
MRI	Magnetic resonance imaging

NMDA	N-methyl-D-aspartate
NSDD	Hypoactive sexual desire disorder
OPC	Oligodendrocyte progenitor cells
ROI	Region of interest
S1	Primary Somatosensory Cortex
SBM	Surface-based morphometry
SE	Standard Error
SD	Sexual Dysfunction
sMRI	Structural magnetic resonance imaging
SPM	Statistical parametric mapping
TMS	Transcranial magnetic stimulation
VBM	Voxel-based morphometry
WM	White matter

Abstract

There is strong evidence for somatotopic organization of cortical representations in the human primary somatosensory cortex. However, the precise location of the somatosensory genital representation field in human females has been controversially discussed for decades. Furthermore, its capacity for structural reorganization as a function of frequency of use has never been studied. In our recently published paper, we combined functional magnetic resonance imaging measures with surface-based morphometry to address the question of somatotopy of the human female genital cortex and its potential for use-associated structural variation depending on frequency of sexual intercourse. We therefore individually mapped the genital representation field via functional magnetic resonance imaging-compatible sensory-tactile stimulation of the clitoral region (versus dorsum of the right hand) in 20 healthy adult females. We next assessed mean cortical thickness across the 10 individually most activated vertices per hemisphere for each woman and correlated mean cortical thickness with frequency of genital intercourse within the past year, taking specific covariates into account.

Functional mapping of the genital cortex revealed significant focal bilateral neural activations in the dorsolateral part of primary somatosensory cortex. These findings provide support for a somatotopically-organized representation of the female genital cortex, in accordance with the anatomical location of the genitals. Correlation analyses yielded a highly significant association between cortical thickness of the individually-mapped left somatosensory genital cortex and frequency of genital intercourse within the past year. These results are the first to report use-associated structural variation of the genital representation field, compatible with the principle of use-dependent cortical plasticity.

This dissertation provides a foundation for future research into experience-related cortical reorganization of the somatosensory genital representation field depending on enriching and aversive sexual sensory experiences and its clinical consequences, such as hypersexual behavior, sexual risk-taking behavior, or sexual dysfunction. It might further have crucial clinical implications for a personalized treatment following exposure to childhood sexual abuse in individuals with pathological conditions.

Zusammenfassung

Eine Vielzahl bedeutender Forschungsbefunde weist auf eine somatotope Organisation kortikaler Repräsentationsfelder im primären somatosensorischen Kortex hin. Die genaue Lokalisation des weiblichen genitalen Repräsentationsfeldes wurde hingegen kontrovers diskutiert. Darüber hinaus ist bisher völlig unklar, ob der genitale Kortex in der Lage ist, sich aufgrund von Erfahrung strukturell zu verändern. In unserem kürzlich publizierten Paper wurden Methoden der funktionellen Magnetresonanztomographie und oberflächenbasierten Morphometrie kombiniert, um die Frage einer somatotopen Anordnung des genitalen Kortex beantworten und dessen Potenzial untersuchen zu können, sich in Abhängigkeit der Häufigkeit sexuellen Verhaltens zu verändern. Hierfür wurde das genitale Repräsentationsfeld bei 20 gesunden, erwachsenen Frauen mittels einer fMRT-kompatiblen sensorisch-taktilen Stimulation der klitoralen Region (versus des rechten Handrückens) auf individueller Ebene lokalisiert. Weiterführend wurde für jede Probandin die gemittelte kortikale Dicke über die 10 am stärksten aktiviertesten Oberflächenpunkte pro Hemisphäre berechnet und mit der Häufigkeit sexuellen Verkehrs innerhalb des vergangenen Jahres korreliert.

Die funktionelle Lokalisation des genitalen Kortex erzielte signifikante fokale bilaterale Hirnaktivierungen im dorsolateralen Teil des primären somatosensorischen Kortex. Diese Befunde stützen eine somatotope Anordnung des genitalen Kortex, in Übereinstimmung mit der anatomischen Lage der Genitalien. Korrelationsanalysen zeigten einen hochsignifikanten Zusammenhang zwischen der kortikalen Dicke des individuell lokalisierten linken genitalen Feldes und der Häufigkeit sexuellen Verkehrs innerhalb des vergangenen Jahres. Diese Befunde deuten erstmals auf strukturelle Veränderungen des genitalen Kortex in Abhängigkeit seiner Nutzung hin.

Diese Doktorarbeit ebnet den Weg für zukünftige Forschung im Gebiet der erfahrungsabhängigen kortikalen Plastizität des somatosensorischen genitalen Repräsentationsfeldes in Abhängigkeit von bereichernden und aversiven sexuellen Erfahrungen und damit einhergehenden behavioralen Problemen, wie hypersexuellem Verhalten, sexuellem Risikoverhalten oder sexuellen Dysfunktionen. Sie könnte außerdem wesentliche klinische Implikationen im Hinblick auf eine personalisierte Behandlung pathologischer Störungen infolge von sexuellen Missbrauchserfahrungen in der Kindheit bereitstellen.

1 Introduction

The human brain has the intrinsic capacity to change its structure as a function of experience across the lifespan. In recent years, a steadily growing body of research has demonstrated use-dependent functional and structural reorganization of the human cortex. However, in addition to the fact that the location of the human female genital somatosensory representation field has been a matter of discussion for decades, is it entirely unknown whether the somatosensory genital representation field is capable to morphologically adapt to the frequency of its use.

In this doctoral thesis, I investigate and establish the precise location of the genital cortex in S1 and provide first evidence on structural variation associated with normative use in adult human females[1].

1.1 The Human Primary Somatosensory Cortex

The human primary somatosensory cortex (S1) is located in the parietal lobe posterior to the central sulcus and underlies sensory-tactile perception[2–4]. It is critical to receiving and processing afferent somatosensory input from the thalamus via the internal capsule[4,5] and to sensorimotor integration[5–7]. Referring to as the postcentral gyrus, S1 receives sensory information from body regions, corresponding to contralateral cortical representations[4]. It is organized into distinct cytoarchitectonic subdivisions, called Brodmann areas (BA), with BA 3b and BA 3a being located in the central sulcus and its caudal bank, BA 1 on the crown of the postcentral gyrus, and BA 2 in the postcentral sulcus[8,9]. While BA 3a gets proprioceptive input from muscles and joints, BA 3b and 1 receive information from cutaneous receptors, and BA 2 integrates the different types of sensory input[10,11]. Sensory information proceeds from rostral to caudal, with increasing receptive fields from BA 3b to BA 2[12,13]. Each of the four cytoarchitectonic areas exhibits a representation of the body[10]. Penfield and colleagues first suggested the principle of somatotopy as a fundamental concept in the structure of S1, providing the foundation for the illustration of the somatosensory homunculus[14–16]. Somatotopy describes that adjacent cortical representations in S1 respond to sensory-tactile stimulation of neighboring or

overlapping body parts[17–19]. The homunculus shows a medial-to-lateral topographical organization, with cortical representations of the lower extremity being located more medially and representations of the upper extremity being located more laterally on the postcentral gyrus[10] (see Figure 1). The size of cortical representations devoted to specific skin sites is proportional to the density of peripheral tactile receptors, leading to cortical overrepresentation of body regions with high sensory-tactile acuity[10,18]. Of note, considerable interindividual variability has been shown regarding the spatial distribution of cortical representations[20]. S1 is structured into six layers, with layer IV neurons receiving thalamic input[4,21] (see Figure 2b).

Functional mapping of the somatosensory cortex has provided strong evidence for somatotopically-organized cortical representation fields for most anatomical dermatomes in humans[22–26]. However hitherto, the precise location of the female genital representation field in S1 is still a matter of discussion[14,27] (see Figure 1).

1.1.1 Functional Mapping of the Human Genital Representation Field

First studies on brain injury at the beginning of the 20th century reported a genital representation between the representations of the legs and trunk[28], while Foerster[29] documented the genital field below the representation of the feet in the paracentral lobule. In the first illustration of the somatosensory homunculus by Penfield and colleagues, the male genital representation field was located posterior to the feet in the mesial wall of S1[15,16], violating the somatotopic order based on its anatomical position adjacent to the hips and above the knees. This so-called non-somatotopic cortical localization of the somatosensory genital representation field had been supported by studies showing functional activations in the paracentral lobule following manual clitoral, vaginal, and cervical self-stimulation[30] and in response to electrical stimulation of the dorsal penile nerve[31–33]. Contradicting a mesial location of the somatosensory genital representation field, it has been shown that S1 does not stretch into the interhemispheric fissure in most humans[34].

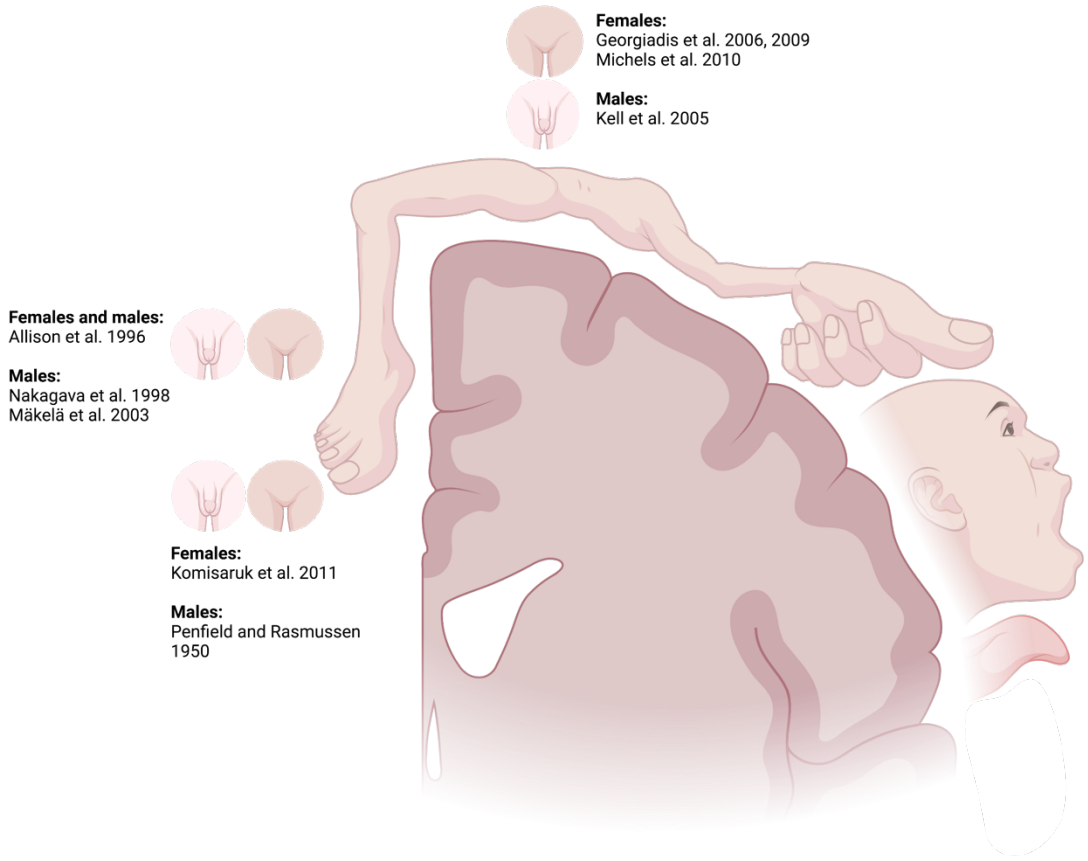


Figure 1. Topographical map of the postcentral gyrus. The somatosensory homunculus delineates which area of the coronal section responds to sensory-tactile stimulation of a specific body region. More mesial parts of S1 represent the lower extremity while dorsolateral parts correspond to enlarged areas of the fingers, face, and mouth, involving high sensory acuity. There are divergent functional mapping results of the human female genital representation field, either being localized in the mesial part or the dorsolateral part of S1 (adapted from Di Noto et al. 2013, p. 1006)[27]. Figure created with BioRender.com.

Evidence for a somatotopic arrangement of genital representation field comes from studies reporting functional activation in the dorsolateral part of S1 following manual stimulation of the clitoris by the partner[35,36], electrical stimulation of the dorsal clitoral nerve[37], and sensory-tactile brushing of the penile shaft[38]. Using ultra-high field 7 Tesla functional magnetic resonance imaging (fMRI), the male genital representation has only recently been located lateral to the feed in S1[39]. These finding are in accordance with evidence from rodent studies mapping the genital cortex in somatotopic organization and bilateral symmetry[40]. The rat genital cortex has been found to be remarkably monomorphic for clitoral and penile input maps, even though external genitals exhibit obvious sexual dimorphism[40,41].

It has been suggested that the type of stimulation used for functional mapping the somatosensory genital field in humans may contribute to diverging findings regarding its precise location. Electrical stimulation is not physiologically valid and has been shown to induce less focal neural activations[42,43]. Partner- or self-applied manual-tactile stimulation likely involves sensations in regions adjacent to the genitals and evokes sexual arousal which may confound the functional response to genital stimulation[30,35,36,44]. The only study which has so far applied a non-arousing sensory-tactile stimulation paradigm was restricted to men[38]. To date, no study has functionally mapped the somatosensory genital representation field in human females, using a non-arousing sensory-tactile stimulation paradigm being compatible to magnetic resonance imaging (MRI), in which neural response to clitoral stimulation is contrasted with stimulation of a control region[1].

1.2 Neural Plasticity of the Adult Human Brain

"Plasticity […] means the possession of a structure weak enough to yield to an influence, but strong enough to yield all at once. Each relatively stable phase of equilibrium in such a structure is marked by what we may call a new set of habits. Organic matter, especially nervous tissue, seems endowed with a very extraordinary degree of plasticity of this sort […]"

William James (1842 – 1910)

Commensurate with William James' theory on plasticity[45] (p. 68), it has become clear that the capacity for functional and structural reorganization is an intrinsic ability of the brain that enables the central nervous system (CNS) to adapt to changing environmental conditions[46,47]. Shaping our neural system, neurons, synapses, and neural networks are able to change as a function of altered afferent input[48,49]. Hebb first stated that learning underlies the strengthening of neural connections based on mutual firing of interconnected neurons[50]. In other words, "*what fires together, wires together*"[51,52]. This Hebbian rule has been widely accepted[53] and is now known as an important principle of experience-driven functional and structural plasticity[54], demonstrating that synaptic input leads to improved signaling via long-term potentiation (LTP)[17,48,53,54] as well as to axonal

and dendritic arborization[48,55,56]. According to the principle of cortical competition, cortical regions enlarge with regular stimulation, while less frequently used cortical areas are narrowed (*"use-it-or-lose-it"*)[54]. A growing body of research suggests that there is remarkable plasticity of the brain depending on experience[46,57], disproving the traditionally held view of the adult brain to be 'hard-wired'.

There is a broad range of MRI studies showing experience-related functional[58–62] and structural[57,63–65] reorganization in the adult human cortex. Using voxel-based morphometry (VBM)[66], Maguire and colleagues were among the first demonstrating an association between the time spent as a taxi driver and bilateral hippocampal grey matter volume (GMV)[67]. Further studies reported sensory GMV effects in musicians as a function of years of practice, showing increased GMV and cortical thickness (CT; see Figure 2a) in auditory cortices[68–73].

Longitudinal structural MRI (sMRI) studies were paving the way for gaining mechanistic knowledge on use-dependent plasticity in sensory and sensorimotor cortices. A groundbreaking study by May and colleagues was one of the first to report increased bilateral GMV in the visual motion area (hMT+/V5) after juggle training[74]. Cortical reorganization has already been shown after seven days of practice[75] and could also be observed in the elderly[76]. An increase in GMV has also been found in the motor cortex following dancing practice, accompanied by increased *Brain Derived Neurotrophic Factor* (BDNF) plasma levels[77], and olfactory cortices following surgical olfactory restoration[78]. Despite volumetric measures, CT estimations have repeatedly been performed to measure experience-related GM structural plasticity. Increased bilateral CT in auditory structures has been associated with piano training[79]. Similar CT effects have been reported for visual processing cortices following dancing exercise[80] and balance training[81] . Findings on whether or not experience-related structural changes are associated with performance are controversial[82]. Interestingly, many structural alterations were limited to the one hemisphere only[77,81].

1.2.1 Experience-Related Plasticity of the Human Primary Somatosensory Cortex

The topographical arrangement of the human S1 underlies the principle of plasticity[4]. There is paramount evidence that the somatosensory cortex changes as a function of use. Experience-dependent somatosensory functional and structural plasticity in humans has been observed after abolishing afferent input from peripheral receptor sites due to limb amputation[83–88] or peripheral nerve damage[89], with phantom limb pain severity being associated with the degree cortical reorganization[84]. In these instances, deafferented representation fields are invaded by adjacent representations of intact sensory input regions[90,91]. Further studies demonstrated that perirolandic cortical reorganization is not only a consequence of peripheral lesion but also related to perceptual stimulation in pain and learning[92–94]. Dinse and colleagues demonstrated that short-term repetitive somatosensory stimulation of the hand leads to increased GMV of the hand representation in S1, being associated with improved tactile perception[95].

Furthermore, functional and structural plasticity in S1 has repeatedly been reported in musicians. Using fMRI, increased S1 activation has been found in the representation of the articulators during classical singing as a function of frequency of use[96] as well as in the representation of the hand during movement execution in string players[97], pianists[98], and trumpet players[99], as compared to amateurs. Increased GMV in the somatosensory hand and foot representations has been reported in professional keyboard players as a function of frequency of practice[100] and altered CT in somatotopic lip and tongue representations of S1 have been associated to intensive musical practice with wind instruments[101]. Long-lasting increased bilateral CT in the somatosensory hand representation has further been demonstrated following intense tactile stimulation during videogame practice[102,103].

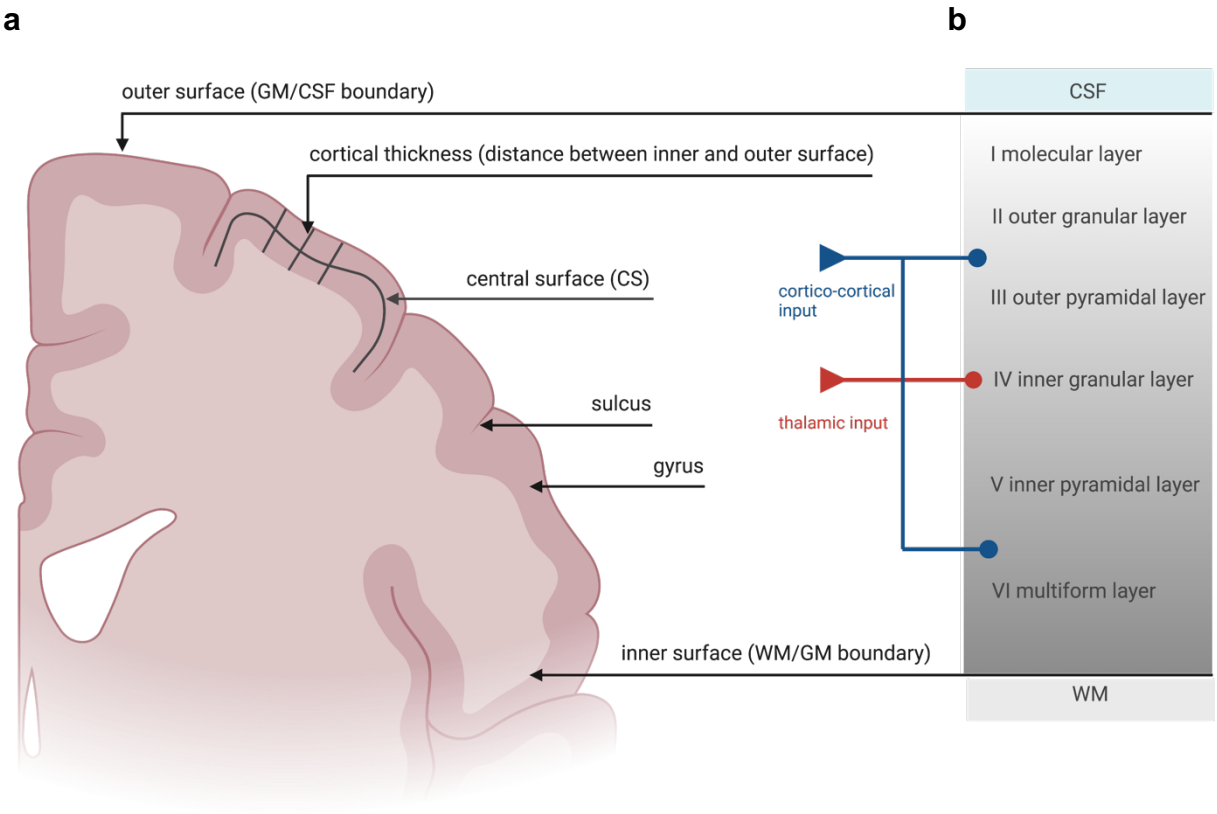


Figure 2. Macroscopic and microscopic illustration of the cerebral cortex and its histological layers. (**a**) The outer surface describes the boundary between CSF and GM, while the inner surface represents the boundary between GM and WM. The central surface (CS) enables a better representation of the cortical sheet and allows for precise surface-based morphometry (SBM). Cortical thickness describes the distance between the inner and outer surface (adapted from Dahnke et al. 2013, p. 2)[104]. (**b**) The cerebral cortex is structured into six layers, with layer IV receiving thalamic input and layers 2/3 and 5/6 being critical for cortical processing of feedforward inputs (adapted from Yu et al. 2019, p. 2)[21]. Figure created with BioRender.com.

While the above cited literature has provided strong evidence in support of somatosensory structural reorganization of cortical representation fields implicated in a specific type of behavior, the capacity for use-associated structural variation of the human somatosensory genital representation field has never been studied and it is entirely unknown as to whether the general principle of use-dependent cortical plasticity applies to the genital field[1].

1.3 Aims of the Dissertation

Combing considerations regarding the precise location of the genital representation field in human females with the notion of structural variation within this region as a function of frequency of sexual intercourse raises an important methodological requirement. In their sensory-tactile stimulation study in men, Kell and colleagues observed a high degree of interindividual variability in the precise location of functional activation within the dorsolateral part of S1[38]. This means that experience-related structural variation of the genital cortex must necessarily be investigated on an individual level to yield sufficient precision. The only study suggesting cortical reorganization of the somatosensory genital representation field following childhood sexual abuse (CSA) in female adults did not individually map the field[105]. Of note, to the best of my knowledge no study has to date investigated structural variation of an individually-mapped cortical sensorimotor representation field in the native space as a function of use. To this end, I conducted my doctoral thesis in the framework of the DFG-funded *SensoCort Study* under Germany's Excellence Strategy (EXC-2049 – 390688087; *SensoCort*).

The aims of this doctoral thesis were:

1) to provide first evidence for a precise location of the individual somatosensory genital representation in adult human females by applying focal sensory-tactile stimulation during fMRI to contrast neural responses of clitoral stimulation versus dorsum manus stimulation. It has been hypothesized that the genital cortex is located in the dorsolateral part of S1, according to the principle of somatotopy.

2) to demonstrate that CT of the individually-mapped somatosensory genital representation field, using the 10 most activated vertices per hemisphere for each woman, varies with frequency of genital intercourse within the past year, suggesting use-dependent plasticity. It has been proposed that there is a positive association between genital field cortical thickness and frequency of genital intercourse.

2 Methods

2.1 Sample

A total sample of 25 adult healthy women aged 18 – 45 years participated in the study. Exclusion criteria included exposure to any type of childhood abuse or neglect, lifetime or current psychiatric or neurological disorders, CNS or urogenital surgery, current severe physical disease, acute or chronic severe stress, any use of psychotropic drugs within the past six months, current menstruation, past or current pregnancy, sexually transmitted diseases, sexual dysfunction (SD; i.e., sexual desire, arousal, orgasm, pain disorders), and dissociation during sexual intercourse. Women were further screened for MRI contraindications. Of those 25 females, 20 participants were included into the analyses. Five participants were excluded due to experimental problems (i.e., technical problems, sensations or numbness in hips and legs during sensory-tactile stimulation paradigm).

2.2 Experimental Procedure

The study comprised a standardized visit at Charité − Universitätsmedizin Berlin. Women underwent standard questionnaires and clinician-administered structured interviews for demographics, sexual orientation, partnership and partnership quality, contraception and menstrual cycle, handedness, as well as for the above-described exclusionary conditions[106–115]. Questionnaires on dissociative experiences during sexual behavior[109] and sexual functioning[113] were translated into German.

In order to investigate use-associated genital field structural variation, women underwent three assessments. We used *1)* fMRI during sensory-tactile stimulation of the clitoral region versus the dorsum of the right hand to map the genital representation field in S1, *2)* sMRI to assess CT of the individually-mapped genital representation field, and *3)* a comprehensive biographic questionnaire on sexual history to assess the frequency of genital intercourse within the past year and in five-year ranges since the onset of first sexual contact. Across participants, mean frequency of genital intercourse was calculated per week for quantification of sexual behavior in the past year and lifetime.

The study was approved by the ethics committee of the Charité – Universitätsmedizin Berlin. All procedures were performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants.

2.3 MRI Acquisition

We performed structural MRI using a 3.0 T Siemens Tim Trio MRI scanner (Siemens Medical System, Erlangen, Germany) with a standard 12-channel head coil. Two 1-mm^3 isotropic T1 images were obtained in the sagittal plane using a magnetization-prepared rapid gradient echo sequence (MPRAGE; TR/TE = 2530/4.94ms, slice number = 176), with a duration of 6:03 min each. Functional MRI was conducted using a T2*-weighted echoplanar image pulse sequence (EPI; TR/TE = 2000/30ms, slice number = 166, voxel size = 3x3x3mm, slice gap = 0.75mm). The sensory-tactile stimulation paradigm during fMRI included four scanning blocks, with a duration of 5:36 min each.

2.3.1 Functional Sensory-Tactile Stimulation Paradigm

A focal non-invasive sensory-tactile stimulation paradigm for MRI was used to measure correlates of neural somatosensory activity in response to sensory-tactile clitoral stimulation. This paradigm was specifically developed and constructed for the current study needs (Prof. Dr. John-Dylan Haynes and PD. Dr. Jürgen Braun; Charité – Universitätsmedizin Berlin). During sensory-tactile stimulation, an air-controlled oscillating membrane with standardized compression was used to apply a precise and focal stimulus on the clitoral region without inducing sexual arousal. For these purposes, women wore disposable underwear. All participants were instructed to position the membrane on the clitoral region below the mons pubis. A Velcro belt was used to fix the device. We performed sensory-tactile stimulation of the dorsum of the right hand to measure neural somatosensory activation in a control region.

The paradigm was conducted in a block design including either clitoral or dorsum manus stimulation, interspersed with 10-second periods without stimulation. The order of

these intervals was fixed and counterbalanced. Each run started with a period of no stimulation and comprised a total of eight stimulation periods of the clitoral region and the dorsum of the right hand, respectively. Presentation (Neurobehavioral Systems Inc., Albany, CA, USA) was used to conduct the stimulation paradigm. During the course of sensory-tactile stimulation, participants were asked to fixate a cross on a screen. One participant completed three runs only.

Seven-point visual analogue scales served to inquire on pleasantness and sexual arousal during sensory-tactile stimulation of the clitoral region after each scanning block. We computed pleasantness and sexual arousal across all scanning blocks after the scan. We further assessed perceived appropriateness of the location of the membrane during sensory-tactile stimulation as well as unintentional sensations in other body parts (i.e., hips and legs). The final sample provided no evidence for sexual arousal or dislocation of the membrane.

2.4 MRI Image Analyses

2.4.1 Functional Mapping of the Genital Representation Field

We used Statistical Parametric Mapping 12 (SPM12; Wellcome Trust Centre for Neuroimaging, University College London, UK)[116] to perform functional imaging analyses. Default spatial preprocessing of functional images was conducted for each scanning block. No participant showed head motion above 3.0 mm of maximal translation in any direction and 1.0 deg of maximal rotation throughout a scanning block. In the following, a general linear model (GLM) was used to analyze fMRI data. The two conditions of clitoral versus dorsum manus stimulation were modelled using a boxcar function convolved with a canonical hemodynamic response function (HRF). Individual maps of functional activation in response to stimulation of the clitoral region versus dorsum of the right hand were obtained by estimating contrasts between the two regressors of the design matrix. We identified distinct neural activations in S1 for each participant, at thresholds of $p < 0.05$ with family-wise error (FWE) correction for multiple comparisons or $p < 0.001$ without correction.

Individual functional activations were overlaid onto co-registered T1 images and saved as regions of interest (ROIs) for each participant for the left and right hemisphere, respectively. We multiplied each individual ROI with the t-score map corresponding to the individual contrast image to show the most activated voxels. With the aim of performing subsequent CT analyses within the individually-mapped ROI in native space T1 images, we did not perform spatial normalization to the MNI (Montreal Neurological Institute EPI template) stereotaxic space or smoothing of functional images by purpose. In order to determine the degree of interindividual variability in the location of the somatosensory genital and dorsum manus representations across participants, coordinates of peak neural activation were spatially normalized to a standard MNI template.

We estimated a random effects GLM across all participants to map the somatosensory genital representation field relative to the representation of the hand on the group level. Therefore, individual contrast maps were spatially normalized and resampled to an isotropic spatial resolution of 3x3x3 mm. Data were further spatially smoothed with a 6 mm full-width at half-maximum isotropic Gaussian kernel. Whole brain random effects models were thresholded at $p < 0.05$ with FWE-correction for multiple comparisons. Coordinates of group-level functional activations in response to sensory-tactile genital and hand stimulation are given in standard MNI space.

2.4.2 Surface-Based Morphometry within the Individually-Mapped Genital Representation Field

We used Computational Anatomy Toolbox 12 (CAT12; Structural Brain Mapping Group, Jena University Hospital, Germany)[117] for SPM12 to conduct surface-based morphometry (SBM) of T1 images. Volumetric segmentation of grey matter (GM), white matter (WM), and cerebrospinal fluid (CSF), including GM-WM and GM-CSF, and spatial registration were performed using an automated procedure with default settings. Subsequently, the ROIs were each separately mapped onto individual cortical surfaces. Surface registration comprised transformation of the individual native space cortical surface of each hemisphere to the *FsAverage* template. After resampling of cortical surfaces to 32k template space, CT at each vertex was estimated, delineating the closest distance between the white matter surface and the pial surface[104,118]. In the following, we separately

calculated mean CT of the 10 functionally most activated vertices within the individually-mapped ROIs for each hemisphere per woman to enable cortical surface measures with maximal precision. Figure 3 outlines CAT12 major processing steps used in our study.

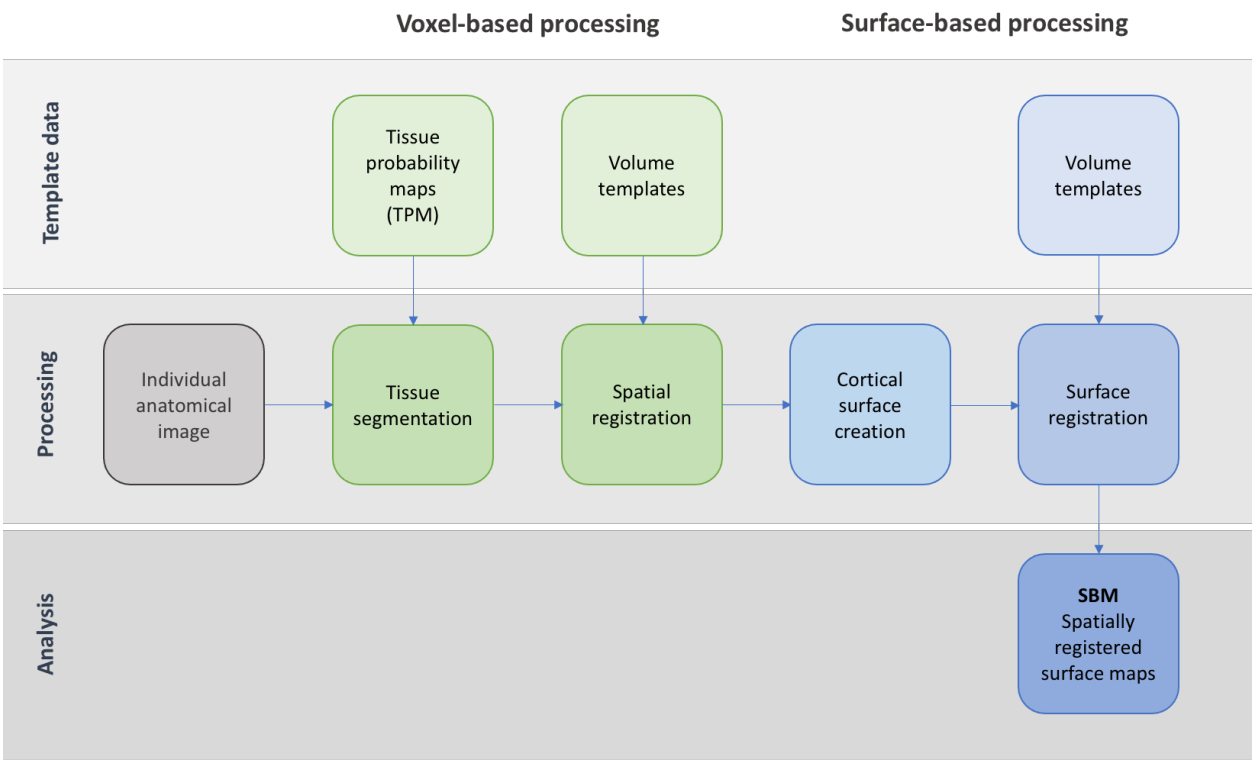


Figure 3. Overview of CAT12 major processing steps. Voxel-based processing comprises tissue segmentation and spatial registration for VBM. Surface-based processing includes cortical surface creation and surface registration for SBM (adapted from Gaser et al. 2022, retrieved January 30, 2023, from https://neuro-jena.github.io/cat12-help/)[117].

2.5 Statistical Analyses

2.5.1 Use-Associated Structural Variation of the Genital Representation Field

We performed partial correlation analyses between genital field CT across the 10 most activated vertices and mean frequency of genital intercourse per week within the past year and since onset of first sexual contact to associate structural variation measures with data on sexual behavior. Age, whole brain CT, and years since the onset of first sexual contact were added as covariates to control for the effects on genital field CT. Because correlation analyses were separately performed per hemisphere, p-values were

adjusted by applying Bonferroni-correction for multiple comparisons. Furthermore, we correlated CT of the left-hemispheric dorsum manus representation across the 10 most activated vertices with frequency of genital intercourse for each time window to provide evidence for regional specificity of experience-related cortical structural variation when controlling for the above covariates. With the aim of testing specificity of the association between genital field structural variation and externally-applied genital touch, we performed partial correlations between genital field CT across the 10 most activated vertices and frequency of genital self-stimulation within the past year, controlling for age, whole brain CT, years since onset of first self-stimulation, and frequency of genital intercourse within the past year. To point out the necessity of conducting cortical surface analyses within an individually-mapped ROI in the native space, partial correlation analyses were conducted between genital field CT across the 10 most active vertices in the MNI space and frequency of genital intercourse for either time window. We ran additional partial correlation analyses using mean CT of the total number of activated vertices per hemisphere per woman, incorporating total individual surface extension.

Statistical analyses and figures were calculated with R Project for Statistical Computing (R Core Team, version 4.0.2), MATLAB (MathWorks, version 9.6), and IBM Statistics (IBM, version 27).

3 Results

3.1 Demographics and Behavioral Data

The study sample (age range 18 – 45 years; mean age ± SD: 23.10 ± 4.35 years) was predominantly European, right-handed, heterosexual, and lived in a monogamous partnership. All women had a higher education. The sample was distributed across menstrual cycle. Characteristics are delineated in Table 1.

Table 1. Characteristics of the study sample.

Age, mean ± SD	23.10 ± 4.35
Ethnicity, *n* (%)	
European	18 (90%)
Middle East	1 (5%)
Asian	1 (5%)
Education, *n* (%)	
Enrolled in university	20 (100%)
Bachelor degree completed	6 (30%)
Master degree completed	2 (10%)
Sexual Orientation[1], *n* (%)	
Heterosexual	17 (85%)
Bisexual	3 (15%)
Homosexual	0 (0%)
Partnership[1], *n* (%)	
Monogamous partnership	14 (70%)
Polygamous partnership	1 (5%)
No partnership	5 (25%)
Contraception and menstrual cycle[1], i (%)	
Hormonal contraception	7 (35%)
Follicular phase	5 (25%)
Ovulation	3 (15%)
Luteal phase	3 (15%)
Irregular menstrual cycle	2 (10%)
Handedness	
Right-handed	18 (90%)
Left-handed	2 (10%)

Values are mean ± SD or *n* (%).
[1]Information derived from self-report.
Note. Adapted from Knop et al. 2022, p. 1135[1]

Self-reports on mean frequency of genital intercourse showed a weekly average of 1.91 (*SD* = 1.30) within the past year and 1.46 (*SD* = 0.93) since the onset of first sexual contact. Of note, behavioral data yielded during the sensory-tactile stimulation paradigm point out that the paradigm was neither unpleasant nor overly pleasant (5.10 ± 0.91). The data further shows that the stimulation did not elicit sexual arousal (4.00 ± 1.41). Behavioral data are shown in Table 2.

Table 2. Behavioral data of the study sample.

Frequency of sexual behavior[1], mean ± SD	
Frequency of genital intercourse/week since onset of sexual contact	1.46 ± 0.93
Frequency of genital intercourse/week within the past 12 months	1.91 ± 1.30
Perceived pleasantness and sexual arousal during sensory-tactile clitoral stimulation[1,2], mean ± SD	
Pleasantness	5.10 ± 0.91
Sexual Arousal	4.00 ± 1.41

Values are mean ± SD or *n* (%).
[1]Information derived from self-report.
[2]Seven-point visual analog scale: 1 = unpleasant / no sexual arousal, 7 = overly pleasant / increased sexual arousal
Note. Adapted from Knop et al. 2022, p. 1135[1]

3.2 Functional Mapping of the Genital Representation Field

Sensory-tactile clitoral stimulation revealed significant focal somatosensory activations. We found neural activations in S1 for all women, with distinctive interindividual variability in the exact location of the functional activation. Sixteen women exhibited bilateral somatosensory activations. For four women, we found neural activation on either the left or the right hemisphere, at thresholds of $p < 0.05$ with FWE correction for multiple comparisons or $p < 0.001$ without correction. Figure 4 shows the individual mapping of peak coordinates of the somatosensory genital representation in the MNI stereotaxic space (classification into Brodmann Areas 3a / 3b, 1 and 2).

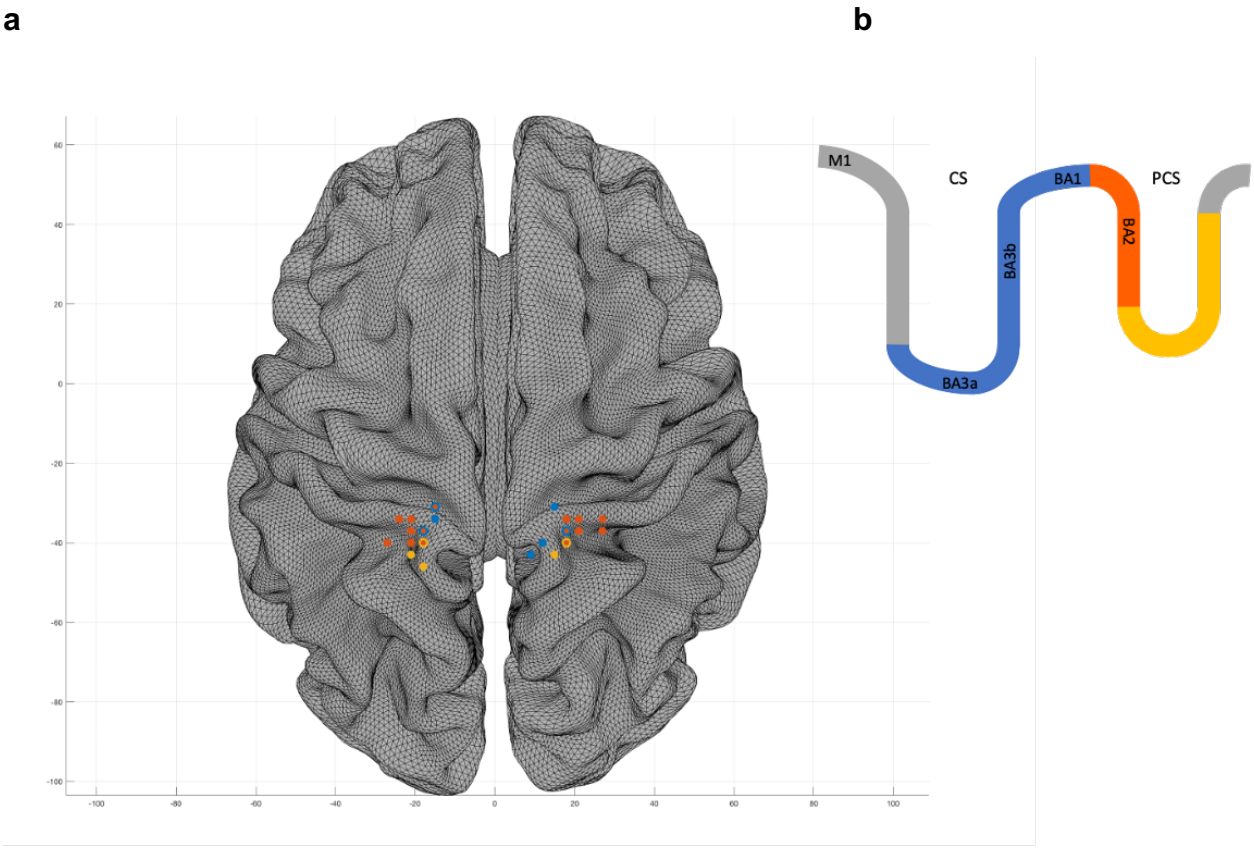


Figure 4. Interindividual variability in the functional mapping of the somatosensory genital representation field in the MNI space. (**a**) Bilateral distribution of individual neural responses to sensory-tactile clitoral stimulation. Brodmann classification was based on probabilistic cytoarchitectonic maps (JuBrain Anatomy Toolbox v3.0; Institut für Neurowissenschaften und Medizin, Forschungszentrum Jülich, Germany[119]). Bi-colored data points indicate overlapping Brodmann areas, depending on the z-coordinate in the transverse plane (see **b**). MNI mean coordinates on the left hemisphere: x = 19.5 (SE: 62.8, range: 27 to 15), y = 38 (SE: 63.6, range: 46 to 31), z = 72 (SE: 64.3, range: 62–80). MNI mean coordinates on the right hemisphere: x = 18.5 (SE: 64.3, range: 9 to 27), y = 38 (SE: 62.8, range: 43 to 31), z = 71.5 (SE: 64.3, range: 62–80). (**b**) Schematic representation of Brodmann areas BA3a, BA3b, BA1, and BA2, indicating that all data points lay within the postcentral gyrus based on the Harvard-Oxford marcoanatomical atlas (adapted from Knop et al. 2022, p. 1136)[1].

Group-level GLM across all participants obtained significant bilateral dorsolateral activations in S1 in MNI the space, when applying a threshold of $p < 0.05$ with FWE correction for multiple comparisons (left hemisphere: x = -18, y = -34, z = 74; $T = 7.72$, $p_{FWE\text{-}corr} = 0.024$; right hemisphere: x = 18, y = -40, z = 68; $T = 10.26$, $p_{FWE\text{-}corr} < 0.0001$). Spatial coordinates indicate the localizations in the x (mediolateral), y (rostrocaudal), and z (dorsoventral) axes. Of note, we did not observe other significant neural responses to clitoral stimulation on the group-level, suggesting that sensory-tactile stimulation specifically targeted the somatosensory genital representation without eliciting sexual arousal. Figure 5 delineates group-level activations mapped onto the cortical surface.

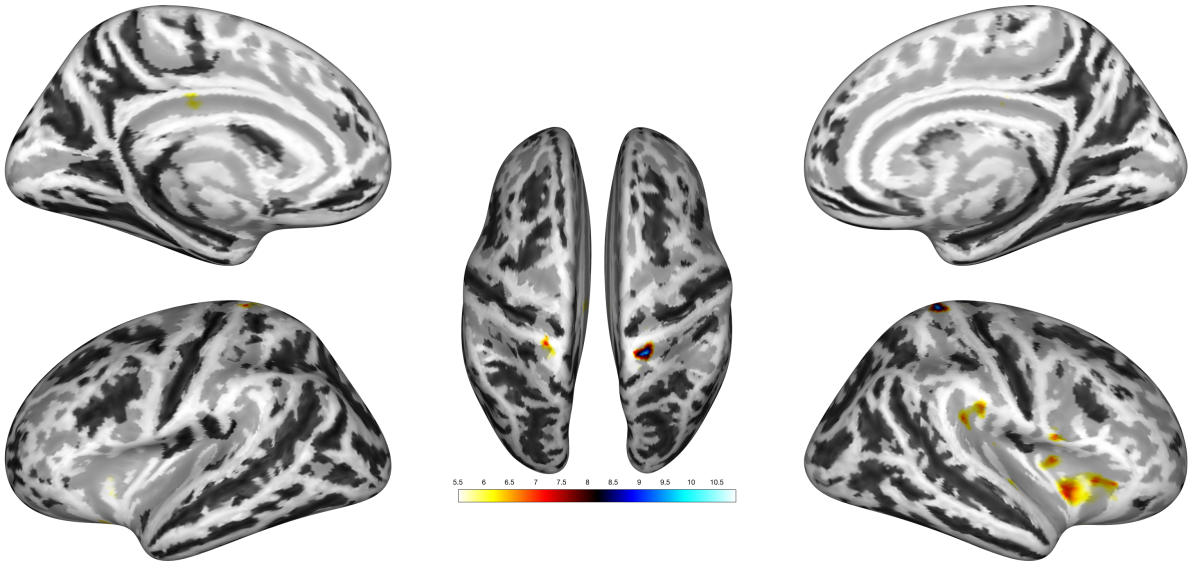


Figure 5. Cortical surface mapping of somatosensory bilateral neural responses to sensory-tactile clitoral stimulation of the random effects GLM. Left hemisphere: x = -18, y = -34, z = 74, right hemisphere: x = 18, y = -40, z = 68; T = 10.26, $p_{FWE} < 0.0001$ (adapted from Knop et al. 2022, p. 1137)[1].

Sensory-tactile right manus dorsum stimulation elicited significant somatosensory activations on the left hemisphere, with considerable individual variability in the precise location of the functional activation. In one woman, we did not observe contralateral functional activation in S1, at thresholds of $p < 0.05$ with FWE correction for multiple comparisons or $p < 0.001$ without correction. Figure 6 delineates the individual localization of peak coordinates of the contralateral somatosensory hand representation in MNI stereotaxic space (classification into Brodmann Areas 3a / 3b, 1 and 2). We did not observe an effect of handedness on location of the hand representation. Group-level GLM across all participants revealed a significant contralateral dorsolateral activation in S1 in the MNI space, following somatotopic sequence relative to the genital field representation, when applying a threshold of $p < 0.001$ without correction (left hemisphere: x = -33, y = -31, z = 62; $T = 6.13$, $p_{uncorr} < 0.001$). Of note, sequential somatotopic representations of the genital field and right hand were found in all women on an individual level as well as at the group-level, commensurate with the location of the dermatomes.

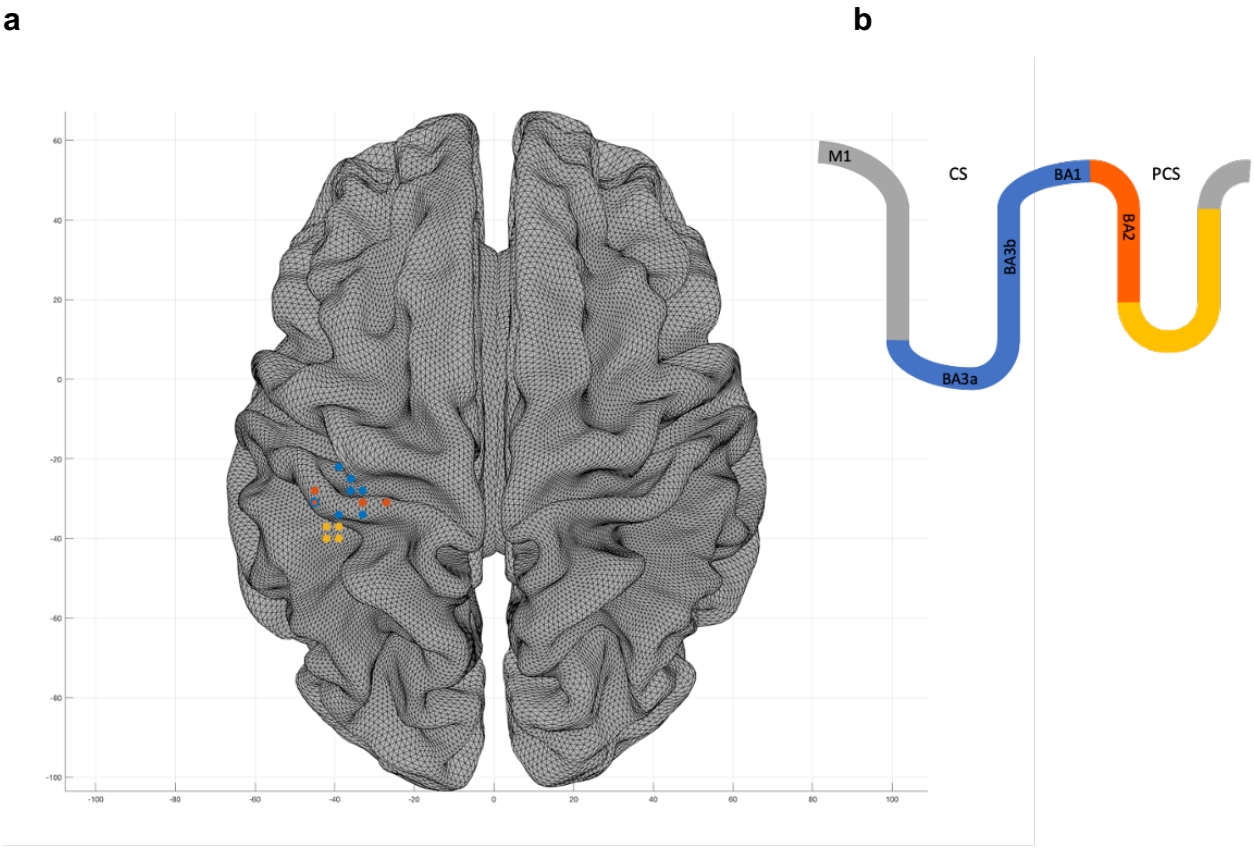


Figure 6. Interindividual variability in the functional mapping of the somatosensory hand representation in the MNI space. (**a**) Contralateral distribution of individual neural responses to sensory-tactile dorsum manus stimulation. Brodmann classification was based on probabilistic cytoarchitectonic maps (JuBrain Anatomy Toolbox v3.0; Institut für Neurowissenschaften und Medizin, Forschungszentrum Jülich, Germany[119]). Bi-colored data points indicate overlapping Brodmann areas, depending on the z-coordinate in the transverse plane (see **b**). MNI mean coordinates on the left hemisphere: x = 38 (SE: 64.3, range: 45 to 27), y = 30.5 (SE: 64.3, range: 40 to 22), z = 62 (SE: 65.0, range: 53–74). (**b**) Schematic representation of Brodmann areas BA3a, BA3b, BA1, and BA2, indicating that all data points lay within the postcentral gyrus based on the Harvard-Oxford marcoanatomical atlas (adapted from Knop et al. 2022, p. 1137)[1].

3.3 Use-Associated Structural Variation of the Genital Representation Field

We estimated mean CT of the 10 functionally most activated vertices within the individually-mapped somatosensory genital representation field per hemisphere per participant. Partial correlation analyses yielded a significant positive association between individual genital field CT on the left hemisphere and frequency of genital intercourse within the past year (r = 0.701, p = 0.004; p < 0.05 Bonferroni-corrected), controlling for age, whole brain CT, and years since onset of first sexual contact. Post-hoc statistical power analysis for the partial correlation between genital field CT and frequency of sexual intercourse within the past year and 3 covariates and an α-level of 0.05, based on the observed effect (r = 0.701), revealed a statistical power of 0.919. Furthermore, a significant

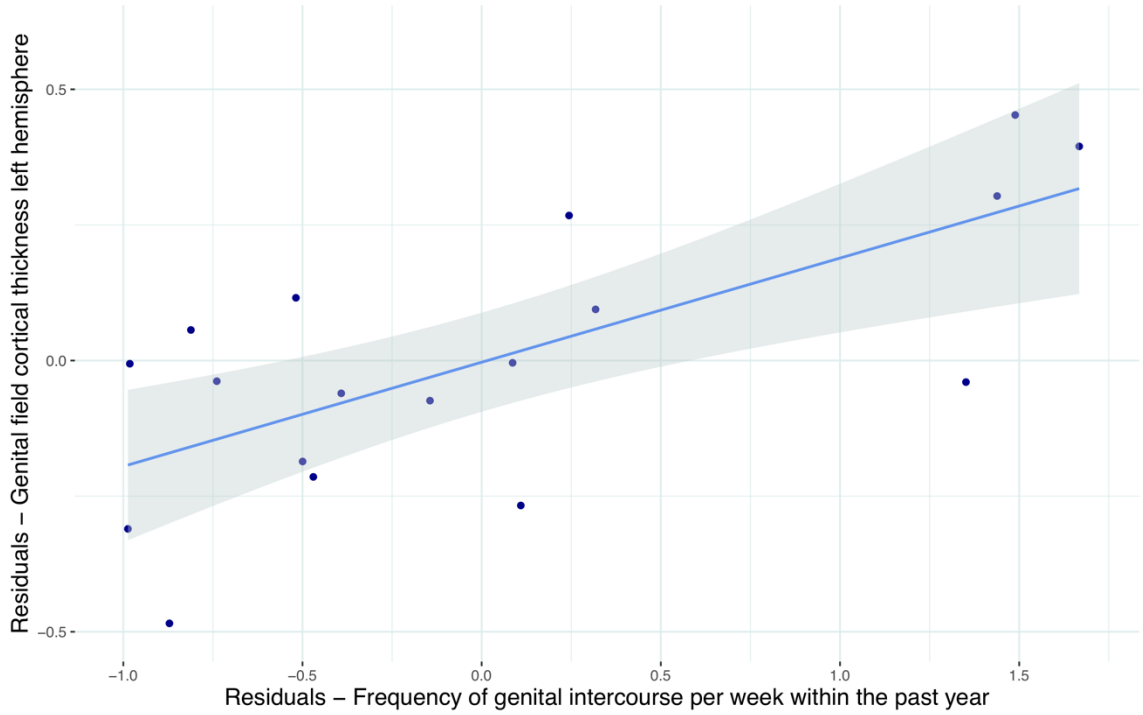
partial correlation was found between left-hemispheric genital field CT and estimated frequency of lifetime genital intercourse since the onset of first sexual contact, while not holding up for Bonferroni-correction (r = 0.538, p = 0.039; p < 0.01 Bonferroni-corrected). Figure 7 demonstrates scatterplots on the association between left-hemispheric genital field CT across the 10 most activated vertices and frequency of genital intercourse within the past year and in lifetime, based on residuals corrected for covariates.

Partial correlation analysis controlling for the above-mentioned covariates did not yield any significant associations between right-hemispheric genital field CT and frequency of genital intercourse for either time window (past year: r = 0.103, p = 0.714; since onset of sexual contact: r = 0.125, p = 0.657), indicating lateralized use-associated genital field structural variation. Furthermore, partial correlation analyses did not reveal any significant results on the association between genital field CT and frequency of genital self-stimulation within the past year (left hemisphere: r = 0.059, p = 0.842; right hemisphere: r = 0.015, p = 0.959), when controlling for age, whole brain CT, years since onset of first self-stimulation, and frequency of genital intercourse within the past year.

We did not find significant partial correlations between left genital field CT in the MNI space and frequency of genital intercourse (past year: r = 0.221, p = 0.428; since onset of sexual contact: r = 0.150, p = 0.593), emphasizing the importance of calculating genital field CT within the individually-mapped ROI in the native space. Of note, partial correlation analyses of mean CT of the total number of activated vertices with frequency of genital intercourse for each time window obtained the same effects, as compared to analyses using the 10 most activated vertices (past year: r = 0.632, p = 0.012; since onset of sexual contact: r = 0.579, p = 0.024). Importantly, menstrual cycle was not associated with genital field CT (left hemisphere: Spearman's ρ = -0.171, p = 0.496; right hemisphere: Spearman's ρ = -0.249, p = 0.320).

We further estimated mean CT of the 10 functionally most activated vertices within the individually-mapped contralateral somatosensory hand representation. Partial correlation analyses between left-hemispheric hand CT and frequency of genital intercourse were conducted, controlling for the above-mentioned covariates. Analyses did not obtain any significant effects for frequency of genital intercourse within the past year (r = 0.344, p = 0.192) or lifetime since onset of first sexual contact (r = 0.228, p = 0.395).

a



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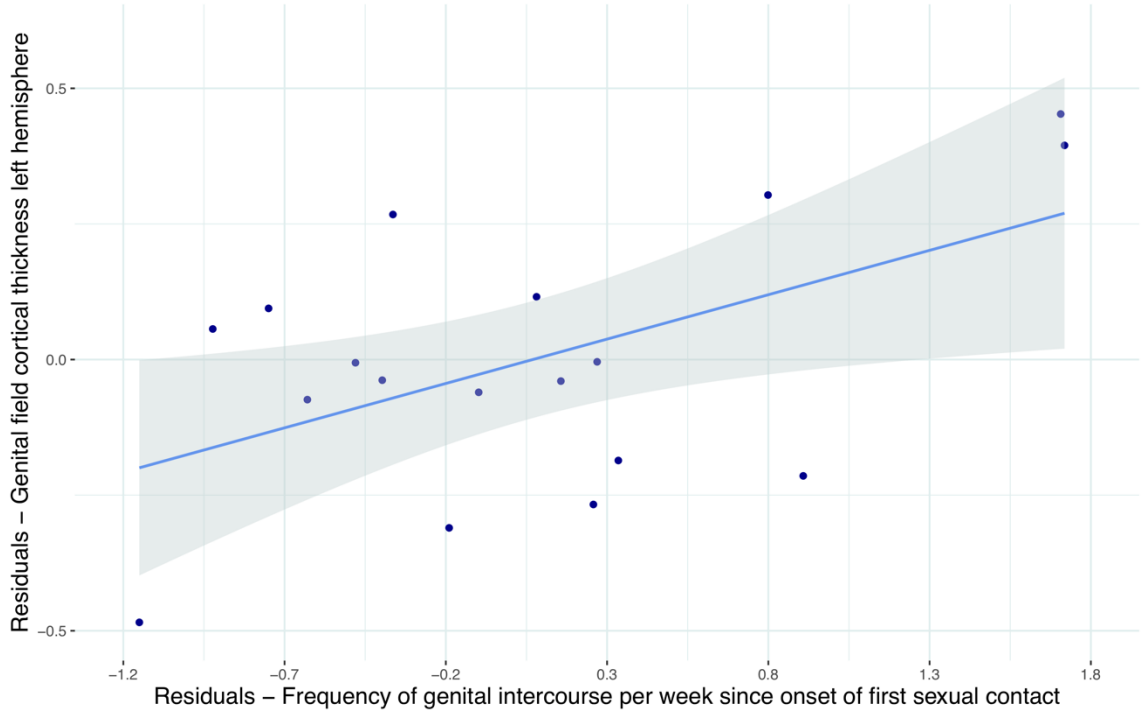

Figure 7. Scatterplots on the correlation between left-hemispheric genital field CT and frequency of genital intercourse per week (**a**) within the past year and (**b**) since onset of first sexual contact. Shaded area denotes standard error (SE). Data points are plotted as residuals corrected for covariates. Partial correlation values of covariates with left genital field CT – age: r = -0.460, p = 0.055, years since onset of sexual contact: r = -0.380, p = 0.120, whole brain CT: r = 0.309, p = 0.213 (adapted from Knop et al. 2022, p. 1138)[1].

4 Discussion

Combining individual functional mapping with innovative cortical surface measures in the female human brain, I present novel results in this dissertation that provide major advances to the field of research. I provide first evidence on the precise location of the human female genital cortex with improved methodological precision and its capacity for use-associated structural variation.

Using an MRI-compatible sensory-tactile non-arousing stimulation paradigm in our study[1], we observed significant focal bilateral dorsolateral functional activation in the post-central gyrus. Of note, there was considerable interindividual variability in the precise location in response to clitoral stimulation with peak functional activations markedly deviating from group coordinates (see Figure 4). These results confirm the traditionally held view that distinct somatosensory regions are responsible for the perception and processing of sensory-tactile stimulation implicated in a specific type of behavior[15,16]. Correlation analyses between structural data and behavioral data on sexual activity provide novel insights into distinct grey matter structural variation of the female genital cortex as a function of mean frequency of genital intercourse within the past year and in lifetime. These results highlight that the adult human cortex has the potential to interact with environmental conditions, compatible with use-associated plasticity[1].

4.1 Functional Mapping of the Genital Representation Field

The exact location of the somatosensory genital representation field in human females has been controversially discussed. Several studies supported a non-somatotopic representation of the genital cortex reporting functional activation in the paracentral lobule[30–33], according to Penfield's topographic map of S1[15,16]. Demonstrating dorsolateral activation in S1, other studies provided evidence in support of a somatotopically-arranged location of the genital cortex, adjacent to the representation of the hips[35–38]. These conflicting results give rise to the question as to whether different methodological approaches in the above studies might have involved confounding factors inherent to the respective stimulation paradigm. The current study solves a controversy surrounding findings from results, by showing several methodological benefits as compared to previous studies[1].

Our results are the first to report a precise location of the female genital cortex, using a focal non-invasive sensory-tactile stimulation paradigm that enables physiological stimulation as opposed to electrical stimulation[31–33]. Sensory foci along the mesial cortex have been suggested to result from artificial electrical stimuli activating enlarged cortical regions as compared to physiological sensory-tactile stimulation[38,42,43]. Electrical cortical surface stimulation used in Penfield and colleagues' historical experiments[15,16] was hardly focal. Simultaneously, contiguous body parts show substantial overlap in cortical activity[2,120], which may have led to impaired differentiation between cortical representations in the lower extremity and the genital region[38]. Indeed, less than 1% of the patients being studied reported precise and distinct genital sensations[16,27,38]. An alternative explanation for mesial cortex activation may assume a top-down control of mentally detecting sensory stimuli. Forss and colleagues showed that neural activation in the paracentral lobule following ulnar and median nerve stimulation is associated with attention being dedicated to sensory-tactile stimuli. While mentally counting nerve stimuli resulted in enhanced mesial cortex activation, ignoring nerve stimuli led to diminished or even vanished mesial functional response[121,122].

Furthermore, our paradigm did not elicit sexual arousal, such that it did not involve manual touch of the genital region in contrast to previous studies applying self-delivered[30] or partner-delivered stimulation[35,36,44]. Remarkably, volume-based group-level analysis confirmed individual mapping results by revealing focal bilateral peak activations on the convexity of the postcentral gyrus, without eliciting significant functional activations in other brain regions. As compared to previous studies[37,38], our results report large statistical effects in terms of particularly high *t*-values, at highest thresholds of statistical significance ($p < 0.05$ FWE corrected for multiple comparisons). These results indicate that our stimulation paradigm did neither elicit sexual arousal nor any uncomfortable feelings. To date, non-arousing sensory-tactile stimulation has only been applied to map the somatosensory genital cortex in males[38].

Due to considerable methodological progress as compared with the above-described previous studies[30,35–37], our paradigm induced focal targeted neural activations without using somatosensory template masks. Our results thus provide unequivocal evidence for the location of the somatosensory genital cortex in human females. Importantly,

our results provide evidence in support of a somatotopically-arranged female genital representation field, adjacent to the representation of the hips commensurate with the anatomy of the body (see Figure 8). Our results correspond to the above-referenced study on the precise location of the genital cortex in human males[38]. Further, our findings are in line with histological mapping data demonstrating a bilateral representation of the genital cortex in S1 as well as a remarkable anatomical monomorphism of cortical penis and clitoral input maps in rodents[40,41,123]. Our study therefore confirms a reconsideration of Penfield's topographic map of S1 by extending validity of a revised homunculus to healthy adult females. Of note, little is known to date about how female body parts are represented in S1 and whether there might be cortical reorganization depending on hormonal stages and experience[27].

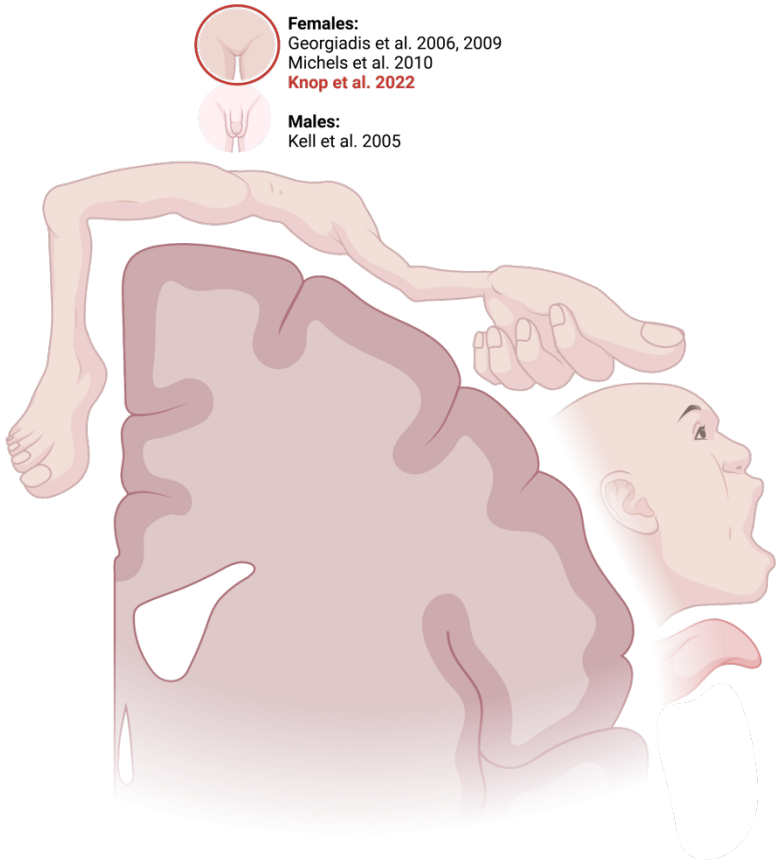

Figure 8. Localization of the female genital cortex in S1, using non-invasive sensory-tactile clitoral stimulation. Functional mapping of the genital cortex revealed significant focal neural activations in the dorsolateral part of S1, bilaterally. These findings confirm a somatotopically-arranged representation of the female genital cortex, adjacent to the representation of the hips commensurate with the anatomy of the body (adapted from Di Noto et al. 2013, p. 1006)[27]. Figure created with BioRender.com.

Although we confirmed a sequential somatotopic representation of the genital representation in each participant, our findings indicate distinctive interindividual variability in the precise location of the genital representation field within the dorsolateral part of S1 in the MNI space[1], as shown in Figure 4. This means that coordinates derived from neural responses to sensory-tactile stimulation of the clitoral region across a group of individuals reflect the mean functional activation in a centered area, while individual peak activations markedly deviate from this group coordinates. Considerable interindividual variability has crucial implications for research, such that it demonstrates the relevance of implementing individual mapping in any study that aims to compute structural data of an individual cortical representation in a precise and reliable manner. Of note, one study suggesting cortical thinning of the genital representation field in S1 after exposure to CSA did not individually map the region[105].

Further, the strength of functional activation and the number of vertices activated by sensory-tactile clitoral stimulation substantially varied across participants. Although the stimulation paradigm was applied with the very same pressure across participants, individual anatomy and placement of the oscillating membrane may have led to variable contact of the membrane with the skin, accounting for variable strength of perception. Thus, we cannot draw valid conclusions about functional plasticity or expansion of the genital field when using a non-invasive air-controlled stimulation paradigm.

To be able to discriminate between neural responses to clitoral stimulation and other body parts, we performed a control task by applying sensory-tactile stimulation of the dorsum of the right hand. Dorsum manus stimulation induced focal contralateral neural activations, localized in the dorsolateral part of S1 in an organized somatotopic sequence with clear distinction to the cortical representation of the genital field (see Figure 6). These results are in line with several studies showing remarkable and fine-grained somatosensory representations of the hand and fingers[11,24,124,125]. Volume-based group-level analysis yielded focal contralateral peak activations in the lateral part of the postcentral gyrus. Interestingly, it has recently been demonstrated that handedness does not account for interindividual variability in the functional localization of the hand representation but does have an effect on the expansion and strength of activation[126].

4.2 Use-Associated Structural Variation of the Genital Representation Field

In first studies, alterations in somatosensory functional activity have been shown after deprivation of peripheral input[127]. Subsequent studies in humans demonstrated use-dependent plasticity in S1 after limb amputation[84,128,129] or peripheral nerve lesion[89]. Since then, it has become clear that our brain is steadily changing its functional and structural properties depending on experience. Studies mapping postnatal brain development from childhood into old age have shown grey and white matter growth and decline in a asynchronous manner[130], supporting the notion that the brain is able to retain its intrinsic potential for neuroplasticity into late adulthood[46,57]. Relying on more recent evidence from studies demonstrating task-specific sensory and sensorimotor structural changes in the adult human brain depending on its use[59,64,46,82,131], we aimed at understanding somatosensory genital field structural variation based on frequency of use. We therefore conducted cortical surface analyses within the individually-mapped ROI, based on the 10 most activated vertices per hemisphere for each participant, to analyze genital field CT with improved methodological precision[1]. Our results are the first to report an association between genital field CT and frequency of sexual intercourse. This association was particularly pronounced for genital intercourse within in past year (see Figure 7a). While less profound, the relationship was also significant for genital intercourse across the lifespan since onset of sexual contact[1] (see Figure 7b). Of note, mean frequencies of more distant and recent sexual intercourse were highly intercorrelated.

Based on the above reasoning, we could not compare the number of activated vertices across participants. Enabling maximal precision, we used the 10 most activated vertices per hemisphere for each participant to identify a ROI that reflects individual peak activation. However, we obtained the same results when calculating correlation analyses using mean CT of the total number of activated vertices per hemisphere for each woman, as compared to using 10 vertices. This indicates a highly robust effect of use-associated genital field structural variation.

Of note, mean frequency of genital intercourse was not correlated with CT of the individually-mapped dorsum manus representation. Further, partial correlations between genital field CT and mean frequency of genital self-stimulation did not yield significance. These results reflect high specificity of use-associated structural variation of the somatosensory genital representation field being implicated in the perception and processing

of externally-applied genital touch. Self-delivered genital touch in contrast to externally-produced genital touch might have different effects on somatosensory cortex activity and structure[132,133]. It has been suggested from the field of motor control that a self-produced action yields a highly accurate prediction of its somatosensory effects, supported by cerebellar activity, which in turn is used to attenuate reactivity of somatosensory areas to the preceding movement. This allows for recognizing motor actions as our own[6,7,132,133]. Such 'forward model' of predicting and attenuating sensory consequences of a self-produced tactile stimulation may not only explain functional neuroimaging results showing a diminished somatosensory response[7,134] but might also serve as a neurobiological mechanism explaining why frequency of self-produced genital stimulation was not associated with increased genital field CT in S1.

Providing novel evidence on structural variation of the genital representation field as a function of frequency of use, our results suggest that the female somatosensory genital cortex might have the capability of adapting in response to environmental conditions, commensurate with the *"use-it-or-lose-it"* concept of Hebbian plasticity[50,54]. Our findings are in line with results from animal studies demonstrating that age-appropriate genital contact results in lateral expansion of the rodent genital cortex[123,135]. Of note, we observed use-associated structural variation of the somatosensory genital field in the left hemisphere only. This effect of lateralization is ambiguous given that functional activation of the female genital cortex was bilateral in our study[1]. However, this left-hemispheric dominance of brain plasticity is in line with recent findings showing learning-dependent cortical changes following musical practice as well as coordination and motor skill training[77,81]. Such lateralization may reflect effects of handedness and hemispheric specialization[136]. Heim and colleagues reported a lateralized effect of genital field cortical thinning after exposure to CSA. They suggested that cortico-limbic modulation of sensory afferents invading into the genital cortex may contribute to unilateral genital field cortical reorganization[105].

Several neurobiological mechanisms might be involved in use-associated structural variation of the genital cortex. Cortical growth may generally be a consequence of neurogenesis, angiogenesis, synaptogenesis, as well as gliogenesis and growth of glial cells[46,48,137–140]. Glutamatergic synaptic transmission has been suggested to play a crucial role in mediating Hebbian plasticity, with *N-methyl-D-aspartate* (NMDA) and *α-amino-3-*

hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors being critical to long-term potentiation (LTP) and long-term depression (LTD)[17,48] as well as dendritic branching and growth of newly added branches[56]. While LTP and LTD represent an underlying mechanism of functional plasticity within a hardwired brain network[141], use-dependent structural changes most likely involve an increase in synapse density driven by axonal sprouting and dendritic spine growth in the mature cerebral cortex[17,46,56,142], accompanied by increased capillary and glial cell density as well as growth of new vascular and glial structures[130,137,143–145]. Animal models assume that axonal and dendritic branching is an adaptive mechanism being associated with enhanced efficiency of processing behaviorally-relevant inputs[46,138–140,146]. Importantly, functional and structural plasticity are interdependent processes involving each other[48,141].

As outlined above, the number of glial cells, i.e. non-neuronal cells, may also contribute to use-dependent MRI cortical volume increase[82]. It has recently been shown in mice that increased exposure to sensory input leads to enhanced myelination within the somatosensory cortex[147], whereas sensory deprivation has been shown to result in cortical hypomyelination[148,149]. Glial cells play a crucial role in coordinating synapse and neural circuit formation[150,151]. While astrocyte activity is crucial for neurovascular coupling and neurometabolism[151–153], oligodendrocytes enable myelination[82,130]. Astrocytes and oligodendrocyte progenitor cells (OPCs) have the capacity to proliferate throughout life[82], with OPCs being associated with formation of new oligodendrocytes[154]. It has been proposed that cell genesis in the adult cerebral cortex is driven by proliferation of neuroglial and endothelial cells[155]. Relying on substantial evidence for experience- and learning-induced gliogenesis and glial growth[143], glial-cell mediated myelination may be mechanism being critical to use-dependent cortical reorganization. It has been shown that cytoarchitectonic alterations often come along with changes in myeloarchitecture, with higher myelin levels in large pyramidal neurons with extensive branching[130]. Thus, lifetime myelination might serve to maintain adaptive and efficient brain functioning. Although oligodendrogensis is very rare in the human adult brain[156,157], high density of premyelinating oligodendrocytes in the human cerebral cortex[158] may enable adaptive myelination to synchronize signal speed to functional demands[159,160]. Interestingly, BDNF which has primarily been known to be implicated in neurogenesis[161,162] and dendritic branching[163,164], has also been shown to be a key pro-myelinating protein by regulating OPCs development[165,166] (see Figure 9). However, whether or not BDNF is involved in use-dependent

myelination is still unknown[82]. Remarkable progress in MRI research will allow for measuring cortical myelin density in specific somatosensory cortical layers and may thus provide novel insights into the underlying mechanisms of cortical reorganization in response to changing environmental sensory input[167,168]. It could be suggested that enhanced frequency of sexual intercourse leads to cortical thickening in somatosensory layer IV that receives sensory thalamic input (see Figure 2b), being associated with increased myelination.

Studies in primates and rodents changing environmental input to primary sensory cortices have been crucial for understanding the driving factors of cortical reorganization[17,135,169,170]. Neuronal functioning of the cerebral cortex has been shown to be dependent on axonal input from the thalamus[48,171]. While dendritic spine numbers of somatosensory cortical neurons are attenuated after removing afferent input[146], invading thalamocortical afferents are associated with an expansion of the female genital cortex in pubertal rodents being exposed to sexual contact[172]. Based on these results, human diffusion tensor imaging (DTI) studies may be critical for elucidating the underlying mechanisms of experience-driven cortical growth and decline.

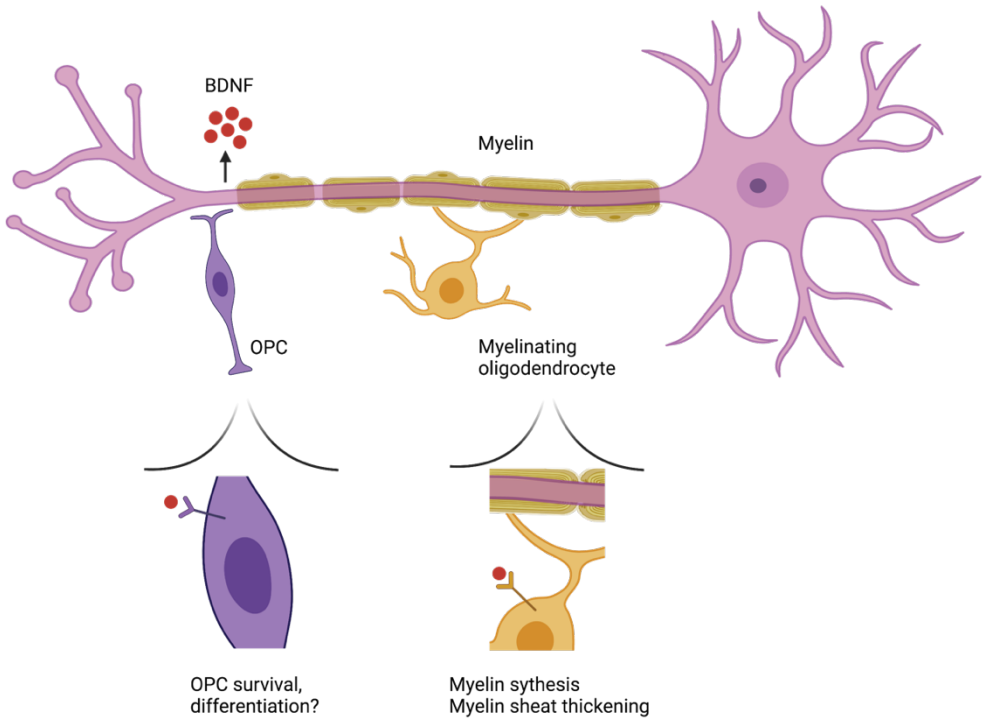

Figure 9. The role of BDNF in cortical myelination. Myelination requires OPCs to differentiate into the mature oligodendrocyte, ensheathing the axon with myelin. Signal transmission results in the release of BDNF along the axon. BDNF signaling is currently discussed in affecting OPC survival and differentiation and plays a key role in the synthesis of myelin, enabling myelin sheat thickening (adapted from Fletcher et al. 2018, p. 3)[166]. Figure created with BioRender.com.

4.3 Strengths and Limitations of this Dissertation

While individual functional mapping of the human female genital field in S1 was conducted experimentally, the examination of genital cortex structural variation associated with sexual behavior depended on retrospective self-report on mean frequency of sexual intercourse. Conceiving the brain as a steadily changing 'system' of which plasticity is both a fundamental condition and a necessary consequence of sensory input or behavioral change[47], cross-sectional studies do not allow for determining as to whether structural plasticity effects are the cause or consequence of experience[1,82,131]. These limitations do not allow for causal interpretation of the results. Nevertheless, our findings clearly provide evidence that external sensory-tactile stimulation is associated with structural variation of sensory cortices that are directly implicated in the respective type of experience. Our results are the first to document an association between structural change of the genital cortex in S1 and frequency of sexual intercourse. Although our underlying sample was relatively small, we found comparatively large correlation effects ($r > 0.5$). This may be based on improved methodological precision by implementing individual mapping of the genital representation field to compute structural data in a precise and reliable manner. The current synopsis expands significantly on the work delineated in the publication. Several analyses are here presented which were not part of the paper.

4.4 Future Research Directions

This dissertation will be critical to developing follow-up studies that aim to elucidate genital field structural reorganization as a function of sexual experiences and pathological conditions of sexual behavior, such as hypersexual behavior, sexual risk-taking behavior, and SD. To establish causality in humans, it will be key to develop prospective longitudinal or quasi-experimental studies, such as monitoring changes in sexual behavior and its effects on somatosensory genital field formation or investigating the effects of sexual therapy on genital field structural changes and sexual behavior. Results from rodent models provide first causal evidence that genital cortex expansion is driven by sensory stimulation of the genitals in pubertal females[135,172].

Furthermore, our results give rise to the question as to whether cortical stimulation, such as transcranial magnetic stimulation (TMS), of the human genital representation in S1 might lead to structural changes which could affect sexual behavior. These results would have substantial clinical impact for individuals suffering from hypoactive sexual desire disorder (HSDD). Extending the sample size and assessing individuals with non-normative sexual behavior will support generalizability of the association between somatosensory genital field structural variation and sexual behavior. Furthermore, using methodological approaches that allow for assessing perception thresholds and estimating cortical expansion of the genital representation field may provide another significant measure of cortical reorganization. Assessing thalamocortical structural connectivity, the degree of myelination within the genital cortex, as well as BDNF plasma levels could provide important insights into the precise underlying mechanisms of experience-driven cortical plasticity of the human genital representation field in S1.

Surprisingly, little is known about the somatosensory cortical representation of *female* body parts in general[27]. Filling this research gap by providing evidence for a female somatotopic map – a so-called *her*munculus – may be crucial for developing targeted treatments for somatosensory disruptions related to female sexual behavior[1] as well as for pain conditions after female surgical interventions[27].

The results of this dissertation further represent an important foundation for a currently conducted translational study which aims at elucidating genital field cortical reorganization and its neurobiological underpinnings as a function of CSA and related sexual-behavioral problems. This study is outlined below.

4.4.1 Experience-Driven Structural Neuroplasticity of the Genital Representation Field after Childhood Sexual Abuse in Female Adults

Although plastic reorganization appears to occur throughout the lifespan[46], the developing brain is markedly more susceptible to the effects of experience[105]. Referring to cortical competition for space[105], it is assumed that plastic changes in the neural system might depend on both the nature and timing of an experience[49,105,173,174]. While enriching

experiences during brain development are suggested to increase its cortical representation[175], developmentally inappropriate experiences are related to cortical narrowing to minimize the detrimental effects on the developing brain[105,176]. The capacity for cortical reorganization during childhood development may thus account for lasting positive effects of developmentally enriching experiences. Elbert and colleagues[175] demonstrated in adult string players that musical practice at an earlier age is associated with an enlarged somatosensory finger representation of the left hand. In recent years, several studies have provided additional evidence on training-induced sensory functional and structural plasticity in childhood[64,177,178]. Similarly, high potential for cortical plasticity may elucidate the long-term negative effects of aversive experiences during childhood. Accordingly, several studies suggest that exposure to childhood maltreatment (CM) specifically impacts cortical sensory representations that are implicated in the perception and processing of the respective aversive experience. Teicher and colleagues report findings on increased GMV in the auditory cortex[179] as well as diminished structural connectivity of the left arcuate fasciculus linking Broca's and Wernicke's area[180] associated with exposure to parental verbal abuse. Furthermore, using whole brain CT analysis, thinning of the visual cortex has been observed after witnessing domestic violence[181]. In a similar vein, Heim and colleagues demonstrated pronounced left-hemispheric genital field cortical thinning in S1 as a function of exposure to CSA in female adults, whereas experiences childhood emotional abuse (CEA) has been associated with cortical thinning of the precuneus and the anterior cingulate cortex being relevant to self-related processes as well as emotional regulation, respectively[105]. The latter study suggested a positive relationship between severity of exposure to CM and the size of effect. A recently published study has further shown that the association between childhood physical abuse (CPA) and depression is specifically mediated by insular activity[182]. These findings give rise to the question on the precise mechanisms underlying regionally-specific cortical sensory reorganization as a function of CM.

Heim and colleagues proposed that such region-specific plastic reorganization may be the brain's most effective response to environmental adversity during development, similar to 'sensory gating' of aversive and developmentally inappropriate sexual sensory experiences at the thalamocortical level. Hence, cortical thinning of the somatosensory genital cortex after exposure to CSA may reflect a highly protective mechanism for the child living in an aversive environment. Simultaneously, it may represent a direct

neural substrate for suffering from behavioral and health consequences later in life when the respective behavior would be expected[105]. Of note, frequent detrimental consequences of CSA in adulthood comprise the development of hypersexual behavior, sexual risk-taking behavior, and SD, including chronic genital or pelvic pain, vaginismus, and dyspareunia as well as orgasm dysfunctions[183–185]. It has been documented that females are more likely to develop SD after CSA than do men, whereas hypersexual behavior has been shown as a consequence of CSA in both women and men[183]. One potential explanation would include that females are more likely to be exposed to penetrative CSA[186].

While the notion of gating abusive sensory experiences remains to be scrutinized, the general concept of thalamocortical gating is a well-established adaptive mechanism of the brain that has been described in terms of a pre-attentive inhibitory response[187–189]. Interestingly, exposure to CSA has been associated to an attenuation of an early implicit electrophysiological response to sexual, trauma-related stimuli[190]. However, sensory gating of sexual aversive input is only one intriguing notion for genital field cortical reorganization after exposure to CSA. The above results may alternatively assume a reverse direction of the effect, such that cortical reorganization occurs as a consequence of behavioral changes following CM. Hence, victims of CSA may avoid sexual contact throughout adolescence and adulthood, which may result in structural plastic processes including diminished thalamocortical connectivity and genital field cortical thinning. Of note, we could clearly demonstrate in humans that genital field structural variation is associated with frequency of sexual intercourse[1]. In contrast, it has been repeatedly reported in humans that female survivors of CSA show rather enhanced sexual activity[191] with earlier onset of sexual intercourse[192], more sexual partners[193], and engagement in risky sexual behavior[194–196]. Of note, Heim and colleagues missed out on assessing sexual behavior in adulthood. Therefore, it is presently unknown whether genital field cortical thinning after CSA indeed is a result of an early sensory gating mechanism, potentially mediated by diminished thalamocortical structural and functional connectivity, or reflects attenuated sexual activity in adulthood. In the absence of data on normative and non-normative sexual behavior, the alternative hypothesis cannot be ruled out. Furthermore, SD has not been assessed to test on whether genital field cortical thinning is associated with SD later in life. Importantly, animal models have not been examining yet whether developmentally inappropriate sexual experiences may lead to enlargement or narrowing of the genital

barrel cortex, compatible with genital field cortical thinning after CSA in adult human females[105].

Based on an asynchronous development of different brain structures in childhood[197], the above-referenced results on regionally-specific cortical reorganization as a function of CM give rise the questions as to whether the effects of CSA might be exceptionally profound during certain developmental periods, in which the brain is particularly susceptible to the effects of experience. Despite the nature and severity of adverse experiences being suggested to affect the outcome, developmental timing may be another crucial factor accounting for the size of effects. According to the framework of developmental programming, particularly high levels of neuroplasticity may be assumed during sensitive developmental periods[197]. That said, there may be discrete time windows throughout childhood, during which aversive exposure may have particularly detrimental and lasting effects on the brain. Teicher and colleagues have identified sensitive time windows for the effects of CM on regional development of the hippocampus, amygdala, and prefrontal cortex[176].

To date, nothing is known about sensitive periods for the effects of CSA on genital cortex development. The identification of such circumscribed time windows may provide an important foundation for the question as to whether timing-dependent effects of CSA on genital field cortical structure are associated with specific symptoms, such sexual risk-taking behavior and SD. Interestingly, Aaron[183] shed light on the questions why one child is affected one way, while another is influenced towards the opposite direction. He reported that the age at onset of victimization is critical to the constellation of symptoms a child develops. That said, the younger the age at onset of exposure of CSA, the more likely the child is to engage in sexual externalizing behaviors later in life. While preschool children are particularly susceptible to developing acting-out behaviors such as sexual aggression and inappropriate sexualized behavior, older children and adolescents show higher risk for internalizing behaviors including sexual withdrawal and inhibition as well as psychological and somatic complaints[198].

To that end, we have been conducting the DFG-funded *SensoCort 2 Study* under Germany's Excellence Strategy (EXC-2049 – 390688087; *SensoCort 2*) in 120 female adults, aged 18 – 45 years, with and without a history of CSA (N = 60 each) since last year. We aim to address the question as to whether genital field cortical thinning is a

result of a protective sensory gating mechanism via diminished thalamocortical connectivity in accordance with developmental programming or a consequence of reduced current sexual activity according to the *"use-it-or-lose-it"* concept. More specifically, we will investigate whether normative structural variation of the somatosensory genital cortex may be overwritten by exposure to CSA and whether genital field cortical thinning is associated with hypersexual behavior, sexual risk-taking behavior, or SD in a state of sensory genital numbness. We further aim to explore the moderating effects of age at onset, severity, and duration of CSA on genital field structural plasticity and connectivity and its clinical consequences. To address the above aims, we seek to compute structural measures of the genital cortex with high methodological precision by adding a functional paradigm of sensory-tactile perception to individually map the genital representation field in S1. This paradigm was established in our recently published study being the key part of my dissertation[1].

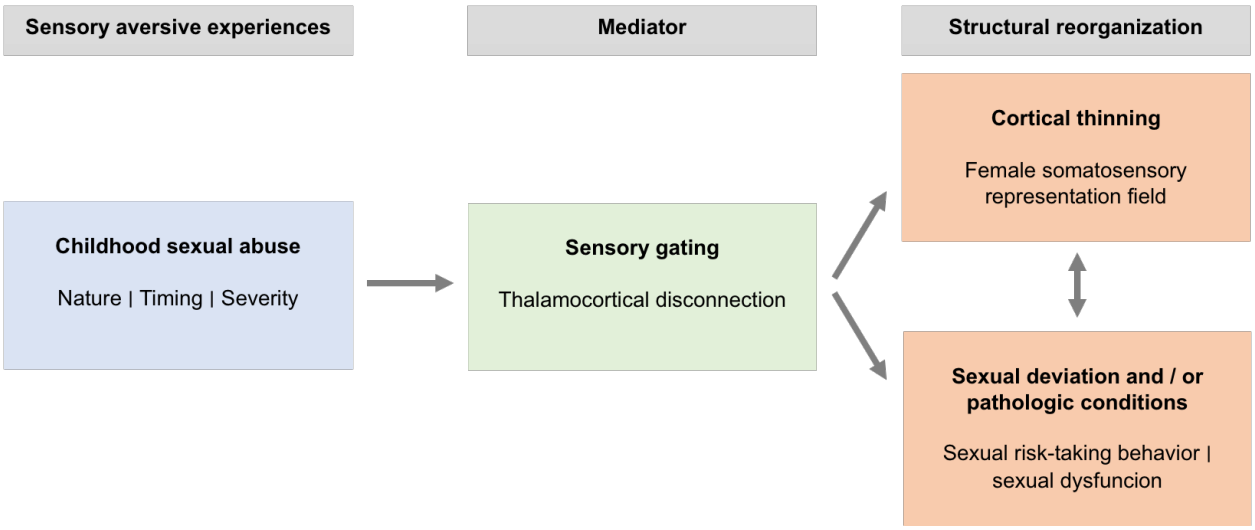

Figure 10. Conceptual Framework of our currently conducted SensoCort 2 Study. We hypothesize that CSA leads to highly-specific cortical thinning of the genital representation field in S1 via gating of sensory aversive experiences that may involve thalamocortical disconnection. We further suggest that genital field cortical thinning may be associated with sexual deviation and / or sexual behavioral problems. Own illustration.

4.4.2 Experience-Driven Structural Neuroplasticity of the Genital Representation Field after Childhood Sexual Abuse in Children

Because the above study is a cross-sectional retrospective study in female adults, the question as to whether genital field cortical thinning following CSA in fact is a result of developmental programming cannot be fully addressed. While there is evidence on an innate somatotopically-organized S1 in humans[199], it is entirely unknown whether cortical development of the human genital representation field in S1 is dependent on hormonal changes during pubertal development and age-appropriate sexual tactile experiences. Rodent models have recently demonstrated that invading thalamocortical afferents are associated with an expansion of the genital cortex following exposure to first sexual contact[172]. Given that there is a gradual increase of input layer 4 neurons in the mouse genital cortex driven by pubertal development and sexual contact[135], age-related genital field cortical increase due to afferent input might also be detected in humans.

With the aim of gaining causal mechanistic knowledge on developmental plasticity of the human somatosensory genital cortex as a result of CSA, prospective studies are essential to test on *1)* whether genital field cortical reorganization might already manifest during childhood, shortly after CSA has occurred, *2)* whether appropriate genital field development is overwritten by these early-life structural changes, and *3)* whether these structural changes are critical to sexual health later in life.

To this end, we are currently planning to investigate genital field CT in children with and without recently documented CSA. For these purposes, we aim to make use of the precise cartography of the genital cortex in human female adults that we established in our recently published study[1]. We further aim to scrutinize whether there is evidence for a sensory gating mechanism that may involve white matter structural disconnection in thalamocortical circuits[48,146]. To test on whether this developmental programming effect is specific to CSA, we plan to also consider data from children with recent physical abuse or neglect. Prospective MRI assessment may enable monitoring the sexual development of children with and without a history of CSA and will further shed light on individual vulnerability to behavioral consequences of CSA.

4.4.3 Clinical implications

This translational research seeks to provide first evidence on the specific impact of CSA on white matter structural disconnection and cortical thinning of the somatosensory genital cortex in adult females and children. We will thus be able to gain novel insights into a neurobiological mechanism of gating sexually aversive experiences from the thalamus to the genital representation field in S1. Monitoring pubertal development and assessing sexual behavior in adolescents will further generate knowledge on specific disruption of stimulators and regulators underlying the maturation and reorganization of a neural network that may by crucial for sexual health development.

These findings will have sustainable effects on future studies and clinical practice by contributing to the understanding of the neurobiological underpinnings of the effects of CSA and its behavioral consequences. Elucidating the impact of CSA on cortical reorganization of the somatosensory genital representation field as an underlying mechanism of the development of pathological conditions, such as sexual risk-taking behavior or SD, might hold the key for devising precise targets and strategies for prevention and intervention in order to minimize the consequences of CSA. Here the challenge will be to determine whether the same neurobiological changes associated with psychopathology may also reflect an adaptive mechanism of the brain ensuring survival of exposure to CSA[176,200].

The identification of sensitive periods for developmental programming effects of CSA may provide an important foundation for developing timing-dependent treatments to take advantage of periods of heightened plasticity and counteract, compensate, or even prevent the neurobiological traces of CSA. Furthermore, deeper knowledge on how sensitive developmental periods are regulated at a molecular level may drive the development of novel pharmacological treatments re-establishing a state of increased plasticity to reprogram the effects of CSA through targeted behavioral intervention[200,201].

5 Conclusions

In this dissertation, I provide unequivocal evidence for the precise location of the human female genital representation field in S1, following a somatotopic sequence and bilateral symmetry. Of note, the underlying publication of my doctoral thesis pointed out considerable interindividual variability in the precise location of the genital representation, suggesting the necessity of computing surface data on an individual level. Based on this reasoning, CT was examined in the individually-mapped somatosensory genital representation. I provide the first proof of principle for use-associated genital field structural variation. These findings support the notion that there may be use-dependent plasticity in the somatosensory genital representation field, albeit the idea of adaptive genital cortex reorganization in response to changing somatosensory input is clearly speculative. However, these research results break ground for future research into somatosensory genital field plasticity as a function of normative or aversive sexual experiences[1]. In current and future studies, our research group aims to scrutinize the mechanisms that drive genital field cortical growth and decline, which may contribute to sexual behavioral-related problems, such as hypersexual behavior, sexual risk-taking behavior, or SD. Such studies will be instrumental to guide the development of novel interventions that specifically target cortical representations of sexual perception and processing in a direct manner.

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Statutory Declaration

“I, Andrea Johanna Julia Knop, by personally signing this document in lieu of an oath, hereby affirm that I prepared the submitted dissertation on the topic Experience-Related Structural Variation in the Human Female Somatosensory Genital Representation Field / Erfahrungsbezogene Strukturelle Veränderungen des Menschlichen Somatosensorischen Genitalen Repräsentationsfeldes bei Frauen, independently and without the support of third parties, and that I used no other sources and aids than those stated.
All parts which are based on the publications or presentations of other authors, either in letter or in spirit, are specified as such in accordance with the citing guidelines. The sections on methodology (in particular regarding practical work, laboratory regulations, statistical processing) and results (in particular regarding figures, charts and tables) are exclusively my responsibility.

Furthermore, I declare that I have correctly marked all of the data, the analyses, and the conclusions generated from data obtained in collaboration with other persons, and that I have correctly marked my own contribution and the contributions of other persons (cf. declaration of contribution). I have correctly marked all texts or parts of texts that were generated in collaboration with other persons.

My contributions to any publications to this dissertation correspond to those stated in the below joint declaration made together with the supervisor. All publications created within the scope of the dissertation comply with the guidelines of the ICMJE (International Committee of Medical Journal Editors; http://www.icmje.org) on authorship. In addition, I declare that I shall comply with the regulations of Charité – Universitätsmedizin Berlin on ensuring good scientific practice.

I declare that I have not yet submitted this dissertation in identical or similar form to another Faculty.

The significance of this statutory declaration and the consequences of a false statutory declaration under criminal law (Sections 156, 161 of the German Criminal Code) are known to me.”

Date Signature

Declaration of your own contribution to the publications

Andrea Johanna Julia Knop contributed the following to the below listed publications:

Publication 1: Knop, A. J. J., Spengler, S., Bogler, C., Forster, C., Brecht, M., Haynes, J.-D. & Heim, C. Sensory-Tactile Functional Mapping and Use-Associated Structural Variation of the Human Female Genital Representation Field, *Journal of Neuroscience* **42,** 1131-1140 (2022).

Contribution (please set out in detail):

I performed extensive background research on the primary somatosensory cortex, the functional localization of the human female somatosensory genital representation field, and on experience-driven plasticity in the human cortex and its underlying neurobiological mechanisms.

Together with my mentors, I was particularly involved in conceptualizing the study and contributed to the application for ethics approval. Furthermore, I had a leading role in performing all the assessments for our study. As an MRI advanced user, I was responsible for the MRI assessments.

I conducted all imaging and statistical analyses under supervision of my mentors and created all figures and tables. I wrote the paper's first draft and actively contributed to all revisions during the publication process.

_____

Signature, date and stamp of first supervising university professor / lecturer

_____

Signature of doctoral candidate

Excerpt from Journal Summary List

Journal Data Filtered By: **Selected JCR Year: 2019** Selected Editions: SCIE, SSCI Selected Categories: **“NEUROSCIENCES”** Selected Category Scheme: WoS **Gesamtanzahl: 271 Journale**

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
1	NATURE REVIEWS NEUROSCIENCE	42,809	33.654	0.055400
2	NATURE NEUROSCIENCE	62,933	20.071	0.144390
3	BEHAVIORAL AND BRAIN SCIENCES	9,395	17.333	0.008170
4	TRENDS IN COGNITIVE SCIENCES	27,705	15.218	0.036050
5	JOURNAL OF PINEAL RESEARCH	10,537	14.528	0.009430
6	NEURON	95,056	14.415	0.199640
7	ACTA NEUROPATHOLOGICA	21,908	14.251	0.040740
8	TRENDS IN NEUROSCIENCES	20,011	12.891	0.021220
9	Annual Review of Neuroscience	13,215	12.547	0.012740
10	MOLECULAR PSYCHIATRY	22,227	12.384	0.054730
11	Nature Human Behaviour	2,457	12.282	0.014190
12	BIOLOGICAL PSYCHIATRY	44,016	12.095	0.053910
13	BRAIN	53,282	11.337	0.067050
14	SLEEP MEDICINE REVIEWS	8,077	9.613	0.013000
15	Molecular Neurodegeneration	4,933	9.599	0.011840
16	PROGRESS IN NEUROBIOLOGY	12,791	9.371	0.011250
17	FRONTIERS IN NEUROENDOCRINOLOGY	4,491	9.059	0.007050
18	ANNALS OF NEUROLOGY	37,304	9.037	0.044120
19	NEUROSCIENCE AND BIOBEHAVIORAL REVIEWS	28,873	8.330	0.051900
20	Neurology-Neuroimmunology & Neuroinflammation	2,232	7.724	0.008400
21	NEUROPATHOLOGY AND APPLIED NEUROBIOLOGY	3,992	7.500	0.005960

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
22	Neurobiology of Stress	1,055	7.197	0.003840
23	NEUROPSYCHOPHARMACOLOGY	26,281	6.751	0.040680
24	npj Parkinsons Disease	662	6.750	0.002500
25	BRAIN BEHAVIOR AND IMMUNITY	16,285	6.633	0.028560
26	Brain Stimulation	6,537	6.565	0.015580
27	NEUROSCIENTIST	5,188	6.500	0.007220
28	Acta Neuropathologica Communications	4,070	6.270	0.014730
29	CURRENT OPINION IN NEUROBIOLOGY	14,959	6.267	0.028730
30	Alzheimers Research & Therapy	3,876	6.116	0.011650
31	Neurotherapeutics	4,998	6.035	0.009520
32	GLIA	14,220	5.984	0.017250
33	NEUROIMAGE	102,632	5.902	0.125360
34	Annual Review of Vision Science	601	5.897	0.003700
35	Molecular Autism	2,510	5.869	0.007450
36	Journal of Neuroinflammation	13,709	5.793	0.025870
37	Translational Stroke Research	2,274	5.780	0.004520
38	JOURNAL OF CEREBRAL BLOOD FLOW AND METABOLISM	19,492	5.681	0.024230
39	JOURNAL OF NEUROSCIENCE	167,114	5.673	0.181170
40	BRAIN PATHOLOGY	5,308	5.568	0.007020
41	Translational Neurodegeneration	1,030	5.551	0.002790
42	NEURAL NETWORKS	14,065	5.535	0.018910
43	PAIN	37,753	5.483	0.035730

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Behavioral/Cognitive

Sensory-Tactile Functional Mapping and Use-Associated Structural Variation of the Human Female Genital Representation Field

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The precise location of the human female genital representation field in the primary somatosensory cortex (S1) is controversial and its capacity for use-associated structural variation as a function of sexual behavior remains unknown. We used a functional magnetic resonance imaging (fMRI)-compatible sensory-tactile stimulation paradigm to functionally map the location of the female genital representation field in 20 adult women. Neural response to tactile stimulation of the clitoral region (vs right hand) identified individually-diverse focal bilateral activations in dorsolateral areas of S1 (BA1–BA3) in alignment with anatomic location. We next used cortical surface analyses to assess structural thickness across the 10 individually most activated vertices per hemisphere for each woman. We show that frequency of sexual intercourse within 12 months is correlated with structural thickness of the individually-mapped left genital field. Our results provide a precise functional localization of the female genital field and provide support for use-associated structural variation of the human genital cortex.

Key words: **functional mapping; genital field; individual variability; plasticity; sexual behavior; somatosensory cortex**

Significance Statement

We provide a precise location of the human female genital field in the somatosensory cortex and, for the first time, provide evidence in support of structural variation of the human genital field in association with frequency of genital contact. Our study represents a significant methodological advance by individually mapping genital fields for structural analyses. On a secondary level, our results suggest that any study investigating changes in the human genital field must map the field individually to achieve sufficient precision. Our results pave the way for future research into the plasticity of the human genital cortex as a function of normal or adverse experience as well as changes in pathologic conditions, i.e., sexual dysfunction, sexual deviation, or sexual risk-taking behavior.

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*J.-D.H. and C.H. shared last authors.

The authors declare no competing financial interests.

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Introduction

The precise location of the female genital representation field in the primary somatosensory cortex (S1) is still a matter of contention (Di Noto et al., 2013; Cazala et al., 2015). Furthermore, the capacity of the human genital representation field for use-associated structural plasticity has never been studied.

In their first presentation of the somatosensory homunculus, Penfield and Rasmussen (1950) placed the male genital field below the foot in the mesial part of S1. This nonsomatotopic location of the genital field was supported by results demonstrating functional activations in the mesial wall of the paracentral lobe in response to electrical stimulation of the dorsal penile nerve in males (Allison et al., 1996; Nakagawa et al., 1998; Mäkelä et al., 2003) and manual-tactile clitoral, vaginal, and cervical self-stimulation in females (Komisaruk et al., 2011). Other studies provided evidence for a somatotopically-ordered representation of the genital field adjacent to the hip and knee areas by demonstrating activations in dorsolateral regions of the postcentral gyrus in response to electrical stimulation of the dorsal clitoral nerve (Michels et al., 2010) or partner-delivered manual stimulation of the clitoris in females (Georgiadis et al., 2006, 2009), as well as sensory-tactile brushing of the penile shaft in males (Kell et al., 2005). These latter results are in line with evidence from rodent studies that localize the rat genital cortex in somatotopic order and bilateral symmetry (Lenschow et al., 2016; Lenschow and Brecht, 2018).

The mode of stimulation used in functional mapping studies may contribute to heterogeneous results concerning the location of the genital field in humans. Specifically, electrical stimulation is not equivalent to sensory touch and elicits less focal responses (Pratt et al., 1980; Forss et al., 1994). Self-delivered or partner-delivered manual stimulation includes touching of areas adjacent to the genitals and elicits sexual arousal that may confound neural response (Georgiadis et al., 2006, 2009, 2010; Komisaruk et al., 2011). The only study using a focal sensory-tactile nonarousing stimulation paradigm in the form of soft brushing of the penile shaft was limited to men and does not inform about female genital field location (Kell et al., 2005). Indeed, no study to date has functionally mapped the female genital field in humans using a magnetic resonance imaging (MRI)-compatible focal sensory-tactile nonarousing stimulation paradigm, contrasting neural response to sensory stimulation of the clitoris against sensory stimulation of a control region.

Commensurate with the fact that the precise location of the genital field remains controversial, there is no evidence regarding its capacity for structural change in association with use in humans. It is well established that the human brain has substantial capacity for plasticity as a function of experience (Draganski and May, 2008). Use-dependent structural reorganization of human S1 has been observed after deprivation of afferent input because of limb amputation (Elbert et al., 1994; Flor et al., 1995; Knecht, 1998) or peripheral nerve lesion (Henderson et al., 2011). Whether or not the human genital field is capable to structurally adapt to its normal use is entirely unknown. Recent evidence suggests that the developing rat genital cortex expands with genital stimulation, facilitating puberty (Lenschow et al., 2017; Sigl-Glöckner et al., 2019).

We here combine the investigation of the location of the female genital field with the question of structural variation of this field as a function of sexual behavior, considering the important issue of individual variability: (1) we provide a precise localization the human female genital representation field by using a focal sensory-tactile nonarousing stimulation paradigm during functional MRI (fMRI) to contrast neural response of stimulation of the clitoral region versus the right hand. (2) We use individually-mapped genital fields based on the 10 most activated vertices per hemisphere for each woman and assess structural thickness in the individually-mapped field using cortical surface analysis. (3) We show that thickness of the individually-mapped genital field varies with the frequency of sexual intercourse in the past 12 months, compatible with use-associated plasticity.

Materials and Methods

Sample

We recruited 25 adult healthy women aged 18–45 years. General exclusion criteria applied to select women were lifetime or current psychiatric disorders, exposure to childhood abuse or neglect (including sexual abuse), neurologic disorders, physical disease, central nervous system or urogenital surgery, psychotropic medication within six months, sexually transmitted disease, sexual disorders (including sexual anxiety, discontent or dysfunction or dissociation during sexual activity), past or current pregnancy, and current menstruation. Exclusionary conditions were assessed using clinician-administered interviews and standard questionnaires (Oldfield, 1971; Hahlweg, 1996; McGahuey et al., 2000; Berner et al., 2004; Kühner et al., 2007; Brenk-Franz and Strauß, 2011; Hansen et al., 2012; Klinitzke et al., 2012; Hoyer et al., 2015; Müller, 2016). Women were screened for contraindications of MRI scanning. Of the 25 women recruited into the study, 20 women were included in the analyses. Five women were excluded because the experimental procedure (i.e., genital stimulation paradigm) was not successful.

Procedure

Women underwent a standardized study visit at the Institute of Medical Psychology and the Berlin Center for Advanced Neuroimaging, both at Charité—Universitätsmedizin Berlin. During the visit, women underwent all study procedures, including interviews and questionnaires for demographics and exclusionary conditions. To localize the genital representation field in S1, women underwent (1) fMRI scanning during sensory-tactile stimulation of the clitoris versus dorsum of the right hand; (2) structural MRI to assess thickness of the individually mapped genital field; and (3) a detailed sexual history to assess frequency of sexual intercourse, i.e., genital sensory touch, in the past year and lifetime for the assessment of use-dependent plasticity of the individually mapped genital field. The study was approved by the institutional ethics committee and was conducted in accordance with the Declaration of Helsinki. Written informed consent of the participants was obtained.

MRI acquisition

Structural MRI was performed using a 3.0 T Siemens Tim Trio MRI scanner (Siemens Medical System) with a standard 12-channel head coil. Two 1-mm^3 isotropic T1 anatomic scans were acquired in the sagittal plane using the magnetization-prepared rapid gradient echo sequence (MPRAGE; TR/TE = 2530/4.94 ms, slice number = 176). Structural MRI acquisition took 2 × 6:03 min. fMRI scans were obtained using a T2*-weighted echoplanar image (EPI) pulse sequence (TR/TE = 2000/30 ms, slice number = 32, voxel size = 3 × 3 × 3 mm^3, slice gap = 0.75 mm). The functional imaging paradigm comprised four scanning blocks with a duration of 5:36 min, respectively.

Experimental design and statistical analysis

Sensory-tactile stimulation paradigm

We developed an MRI-compatible sensory-tactile stimulation paradigm that allows for administering a defined focal sensory stimulus to the clitoral region (see Fig. 1). The stimulation was administered using a noninvasive air-controlled oscillating membrane with a compression of ~0.1 bar. Women were asked to place the membrane below the mons pubis on the clitoral area above standardized disposable underwear. The sensory-tactile device was fixed with elastic tape and a flexible Velcro belt. Sensory-tactile stimulation of the dorsum of the right hand was used as a control condition, given that the S1 representations of the

Figure 1. Device for sensory-tactile stimulation of the clitoral region and dorsum of the right hand. The stimulus is delivered via a noninvasive air-controlled oscillating membrane with a compression of ~0.1 bar.

dermatomes of the genital region and the hand are well distinguishable (Roux et al., 2018).

The paradigm was performed in an ABBA versus BAAB block design with stimulation of either the clitoral region (A) or the dorsum of the right hand (B) interspersed with 10-s periods of no stimulation. Each of the four runs started with a period of no stimulation and included a total of eight clitoral and eight dorsum manus stimulation phases. The order of these phases was fixed and counterbalanced between women. Synchronization of the trigger pulses from the MRI scanner and the timing of the stimulation was controlled using Presentation (Neurobehavioral Systems Inc.). During the sensory-tactile stimulation, subjects were asked to fixate a cross on a screen. One woman completed only three runs.

Pleasantness and sexual arousal during clitoral stimulation were assessed after each run using a seven-point visual analog scale. Subjects were instructed to use a fiber-optic response box, indicating changes in pleasantness and sexual arousal. We then computed combined ratings on overall pleasantness and sexual arousal after the scan. We further inquired on the subjective appropriateness of the location of the clitoral membrane during the experiment as well as on sensations in other body parts during clitoral stimulation. There was no evidence for dislocation of the stimulation membrane in the sample.

Localization of genital field

Statistical parametric mapping 12 (SPM12; Wellcome Trust Center for Neuroimaging, University College London, London, United Kingdom) was used to perform functional image analysis to localize the genital field in S1. Standard spatial preprocessing of functional images, including realignment and coregistration to T1 image, was separately performed for each of the four scanning blocks. Data were high-pass filtered with a default cutoff period of 128 s to correct for slow drift artifacts. There was no head motion above 3.0 mm and 3.0° of maximal translation and rotation in any direction throughout a scanning block.

After standard spatial preprocessing, fMRI data were analyzed using a general linear model (GLM). The two within-subject conditions of interest (10 s of either clitoral or hand stimulation alternating with 10 s of rest) were modeled using a boxcar function convolved with a canonical hemodynamic response function (HRF). Activation maps were calculated with *t* tests for contrasts between the two regressors of the design matrix, resulting in individual patterns of neural activation in response to clitoral versus hand stimulation. We identified an activated region in SI for each participant at $p < 0.001$ without correction or $p < 0.05$ with family-wise error (FWE) correction for multiple comparisons. Individual neural activations were overlaid onto coregistered anatomic scans and saved as individual regions of interest (ROIs) for the left and right hemisphere, respectively. Individual ROI was multiplied with the t-score map corresponding to the individual contrast image to delineate the most activated vertices within the individually defined ROI. We purposely did not perform spatial normalization to a standard stereotaxic space (Montreal Neurologic Institute EPI template; MNI) or smoothing of the images to allow for subsequent cortical thickness analyses within the individually mapped ROI in native space of the anatomic images, as needed for the use-dependent plasticity analyses. To determine variability of the location of the genital field and hand representation in S1 between women, coordinates of peak neural activation were transformed in MNI space. Barycentre and dispersion across individually mapped fields were computed by averaging individual coordinates in MNI space.

To additionally localize the genital representation field in S1 on the group level, a random effects GLM was estimated across subjects. For this, individual contrast maps were spatially normalized to a standard MNI template and resampled to an isotropic spatial resolution of $3 \times 3 \times 3$ mm^3. Furthermore, data were spatially smoothed with a 6-mm full-width at half-maximum isotropic Gaussian kernel. Whole-brain group-level analysis with *t* tests contrasting neural response to the two with-subject factors genital stimulation versus stimulation of the dorsum of the right hand was thresholded at $p < 0.05$ with FWE-correction for multiple comparisons. Coordinates of the group-based neural activation reflecting the genital field are given in standard MNI space.

These statistical analyses and figures were computed using MATLAB (MathWorks, version 9.6.)

Anatomical image segmentation and surface-based morphometry (SBM; CAT12)

Automated image segmentation included (1) spatial registration (affine registration to tissue probability map); (2) initial SPM unified segmentation and skull stripping; (3) local intensity transformation to reduce tissue inhomogeneities (local adaptive segmentation; Dahnke et al., 2012); (4) volumetric segmentation of gray matter (GM), white matter (WM), and CSF, as well as GM-WM and GM-CSF, providing a more accurate segmentation (Tohka et al., 2004); (5) spatial normalization/DARTEL registration (Ashburner, 2007); (6) central surface estimation (projection-based thickness method; Dahnke et al., 2013); (7) topology correction (Yotter et al., 2011a); (8) surface inflation (spherical mapping; Yotter et al., 2011b) and spherical atlas registration (resampling; Yotter et al., 2011c), and default merging of hemispheres.

Thickness of individually mapped genital field

The Computational Anatomy Toolbox 12 (CAT12; Christian Gaser, Structural Brain Mapping Group, Jena University Hospital, Jena, Germany) for SPM12 was used to perform cortical SBM of the anatomic scans. Image segmentation was conducted using an automated standard procedure. The individually defined ROIs for the clitoris and the dorsum of the right hand were separately mapped onto individual native space cortical surfaces of the left and right hemisphere. After cortical surface registration, mean thickness of the 10 functionally most active vertices within the individually mapped ROIs was separately calculated for each hemisphere in each woman. Cortical thickness at each vertex was calculated as part of central surface estimation (Dahnke et al., 2013), describing the closest distance between the inner surface (WM/GM boundary) and the outer surface (GM/pial boundary) at each vertex of the tessellated brain surface (Fischl and Dale, 2000; Dahnke et al., 2013).

Use-associated structural variation of the genital field

We assessed mean frequency of sexual intercourse per week using a standardized biographic questionnaire to quantify sexual intercourse within the past 12 months and in five-year ranges since the onset of the first sexual genital contact. As noted above, we excluded sexual anxiety, discontent or dysfunction as well as dissociation during intercourse using established questionnaires (McGahuey et al., 2000; Berner et al., 2004; Brenk-Franz and Strauß, 2011; Hansen et al., 2012; Hoyer et al., 2015; Müller, 2016). To associate cortical thickness measures of the

Table 1. Characteristics of the sample and behavioral data ($N = 20$)

Age, mean ± SD	23.10 ± 4.35
Ethnicity, *n* (%)	
European	18 (90%)
Middle East	1 (5%)
Asian	1 (5%)
Education, *n* (%)	
Enrolled in university	20 (100%)
Bachelor degree completed	6 (30%)
Master degree completed	2 (10%)
Sexual orientation[1], *n* (%)	
Heterosexual	17 (85%)
Bisexual	3 (15%)
Homosexual	0 (0%)
Partnership[1], *n* (%)	
Monogamous partnership	14 (70%)
Polygamous partnership	1 (5%)
No partnership	5 (25%)
Sexual behavior[1], mean ± SD	
Frequency of sexual intercourse/week since onset of sexual contact	1.46 ± 0.93
Frequency of sexual intercourse/week within the past 12 months	1.91 ± 1.30
Perceived pleasantness/sexual arousal during sensory-tactile clitoral stimulation[1,2], mean ± SD	
Pleasantness	5.10 ± 0.91
Sexual arousal	4.00 ± 1.41
Contraception and menstrual cycle[1], i (%)	
Hormonal contraception	7 (35%)
Follicular phase	5 (25%)
Ovulation	3 (15%)
Luteal phase	3 (15%)
Irregular menstrual cycle	2 (10%)
Handedness[1], *n* (%)	
Right-handed	18 (90%)
Left-handed	2 (10%)

Values are mean ± SD or *n* (%).
[1] Information derived from self-report.
[2] Seven-point visual analog scale: 1 = unpleasant/no sexual arousal, 7 = overly pleasant/increased sexual arousal.

individually mapped genital field with data on sexual behavior, we correlated individual cortical thickness with the mean frequency of sexual intercourse per week within the past 12 months. We further correlated cortical thickness of the individually mapped genital field with the frequency of sexual intercourse estimated across a longer time period since the first onset of sexual contact. As we calculated one correlation per hemisphere, we did apply a Bonferroni-correction for multiple comparisons to the results ($\alpha_{corr} = 0.025$). Using partial correlation analyses, we used age, years since onset of sexual contact, and whole-brain cortical thickness as covariates to control for effects of these variables on genital field cortical thickness. Furthermore, correlations and partial correlations between left-hemispheric cortical thickness of the representation field of the right hand and frequency of sexual intercourse for either time window were calculated to confirm for region-specificity of use-associated variation. These statistical analyses and figures were computed using R Project for Statistical Computing (R Core Team, version 4.0.2) and IBM SPSS Statistics (IBM, version 27).

Data availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Code accessibility

Custom MATLAB Code (version R2018b, MathWorks) for SPM12 and CAT 12 will be provided on request.

Results

Demographic and behavioral data

Demographic and behavioral data are presented in Table 1. Mean age of the sample was 23.10 years (SD = 4.35). The majority of women was of European descent, had a higher education, were heterosexual, lived in a monogamous partnership, and were right-handed. Seven women were on oral contraceptives. MR scans were distributed across menstrual cycle phase. Mean frequency of sexual intercourse in the past 12 months was reported to have been 1.91 times per week (SD = 1.30). Mean frequency of sexual intercourse since the onset of sexual contact was reported to have been 1.46 times per week (SD = 0.93). Importantly, behavioral data obtained during the sensory-tactile stimulation paradigm confirmed that the stimulation was not unpleasant and neither overly pleasant nor overly sexually arousing.

Functional mapping of the female genital field: neural response to sensory-tactile stimulation

Sensory-tactile stimulation of the clitoral region (relative to right hand) induced significant focal neural activations in S1. Sixteen women exhibited bilateral neural activations in S1. For four women, a significant activation was found in either the right or the left hemisphere only. Table 2 delineates individual MNI coordinates with the respective p value thresholds and t scores of the sensory foci for clitoral stimulation. Individual focal neural activations occurred in Brodmann areas 1, 2, and 3a/3b (BA1–BA3) of the postcentral gyrus for all women. Within BA1–BA3, there was distinctive individual variability of the precise location of the neural activation in response to stimulation of the clitoral region. Figure 2 shows the individual localization of the clitoral somatosensory representation in normalized stereotaxic coordinates (MNI space).

We next mapped the individual representation of the dorsum of the right hand for use in subsequent cortical thickness analyses. Sensory-tactile stimulation of the dorsum of the right hand (relative to clitoral region) induced significant contralateral focal neural activations in S1. Table 2 delineates individual MNI coordinates with the respective p value thresholds and t scores of the sensory foci for the stimulation of the right hand. Individual focal neural activations occurred in BA1–BA3 of the postcentral gyrus, with individual variability of the precise location of the neural activation. Figure 3 shows the individual localization of the somatosensory representation of the hand in normalized stereotaxic coordinates (MNI space) for the left hemisphere. There was no significant effect of handedness on functional activation of the hand representation. Of note, the location of the representation field of the clitoris and the representation field of the hand was somatotopically-ordered for each woman and commensurate with anatomic location.

When analyzed at the group level across all women, GLMs revealed significant symmetric dorsolateral neural activations in S1 in response to stimulation of the clitoris (relative to hand) in both hemispheres (left hemisphere: $x = -18$, $y = -34$, $z = 74$; $T = 7.72$, $p_{FWE\text{-}corr} = 0.024$; right hemisphere: $x = 18$, $y = -40$, $z = 68$; $T = 10.26$, $p_{FWE\text{-}corr} < 0.0001$). Of note, no other significant neural activations were observed at the group level in response to the stimulation of the clitoral region, suggesting that the stimulation paradigm specifically targeted the genital field and was not overly arousing. Figure 4 shows normalized stereotaxic coordinates (MNI space) for the group location mapped onto the cortical surface.

Use-associated structural variation of the female genital field: SBM

We mapped individual ROIs for the genital field (representing the 10 most activated vertices per hemisphere during clitoral stimulation) onto native cortical surfaces for each subject and

Table 2. Individual and group cortical activations in response to sensory-tactile stimulation of clitoris or dorsum of the right hand

	Genital representation Left hemisphere				Genital representation Right hemisphere				Hand Representation Left hemisphere			
Single subject	Center of gravity (*x*, *y*, *z*)	*t* value	*p* threshold	Cortical thickness	Center of gravity (*x*, *y*, *z*)	*t* value	*p* threshold	Cortical Thickness	Center of gravity (*x*, *y*, *z*)	*t* value	*p* threshold	Cortical thickness
1	−21, −40, 74	14.48	FWE 0.05	2.3309	18, −40, 80	5.75	FWE 0.05	2.5585	−42, −37, 59	4.92	FWE 0.05	2.9968
2	−24, −34, 77	3.35	Uncorr. 0.001	2.0890	15, −31, 71	2.26	Uncorr. 0.001	1.5174	−33, −31, 68	1.68	Uncorr. 0.001	2.4194
3	—	—	—	—	15, −43, 62	3.22	Uncorr. 0.001	2.1214	−27, −31, 68	4.56	FWE 0.05	2.4300
4	−18, −40, 62	10.12	FWE 0.05	2.2791	—	—	—	—	−39, −34, 65	4.50	FWE 0.05	2.3970
5	−18, −46, 68	4.83	Uncorr. 0.001	2.1010	—	—	—	—	−39, −40, 62	2.70	Uncorr. 0.001	2.8083
6	−21, −40, 71	3.01	Uncorr. 0.001	2.5363	18, −37, 71	6.00	Uncorr. 0.001	2.1836	−36, −28, 65	4.26	FWE 0.05	1.7383
7	−21, −34, 80	9.01	FWE 0.05	2.2215	27, −34, 71	17.29	FWE 0.05	1.7881	−45, −31, 62	13.59	FWE 0.05	2.2301
8	−21, −40, 71	14.13	FWE 0.05	2.4748	21, −37, 71	10.29	FWE 0.05	2.7262	−39, −22, 65	3.81	FWE 0.05	2.1545
9	−15, −34, 71	4.62	Uncorr. 0.001	2.3893	18, −37, 65	6.31	Uncorr. 0.001	2.0032	—	—	—	—
10	−15, −31, 65	7.06	Uncorr. 0.001	2.4279	18, −40, 74	7.68	Uncorr. 0.001	2.6370	−36, −28, 65	2.68	FWE 0.05	2.1161
11	−18, −40, 68	11.76	FWE 0.05	2.6785	18, −34, 74	10.04	FWE 0.05	2.0501	−36, −25, 65	8.55	FWE 0.05	2.3915
12	−21, −37, 77	7.68	Uncorr. 0.001	2.4222	21, −37, 68	12.56	Uncorr. 0.001	2.1976	−42, −37, 56	7.05	FWE 0.05	2.3930
13	—	—	—	—	27, −37, 71	3.34	Uncorr. 0.001	2.2787	−42, −40, 56	5.38	Uncorr. 0.001	2.7626
14	−15, −31, 77	4.52	Uncorr. 0.001	1.7867	12, −40, 71	10.24	Uncorr. 0.001	2.0809	−33, −28, 62	4.93	Uncorr. 0.001	1.5778
15	−18, −37, 68	6.99	FWE 0.05	2.2393	18, −40, 80	8.92	FWE 0.05	2.3916	−45, −31, 56	2.57	Uncorr. 0.001	2.8190
16	−21, −40, 74	6.46	FWE 0.05	2.0462	21, −34, 77	9.89	FWE 0.05	2.2819	−33, −34, 53	2.31	Uncorr. 0.001	1.9530
17	−21, −43, 71	3.84	Uncorr. 0.001	2.8488	09, −43, 68	4.66	Uncorr. 0.001	2.3182	−45, −28, 62	3.21	FWE 0.05	2.8617
18	−18, −37, 74	6.46	FWE 0.05	2.4128	18, −37, 71	7.80	FWE 0.05	2.5398	−36, −28, 59	3.06	Uncorr. 0.001	1.6492
19	−18, −37, 74	7.48	FWE 0.05	1.8379	18, −40, 71	17.96	FWE 0.05	2.0445	−39, −37, 62	7.24	FWE 0.05	2.1116
20	−27, −40, 71	2.83	Uncorr. 0.001	2.6396	18, −40, 71	5.80	Uncorr. 0.001	2.3120	−36, −28, 65	2.25	Uncorr. 0.001	1.7425
Group	Center of gravity (*x*, *y*, *z*)	*t* value	*p* threshold		Center of gravity (*x*, *y*, *z*)	*t* value	*p* threshold		Center of gravity (*x*, *y*, *z*)	*t* value	*p* threshold	
	−18, −34, 72	7.72	FWE 0.05		18, −40, 68	10.26	FWE 0.05		−33, −31, 62	6.13	Uncorr. 0.001	

Coordinates indicate the somatosensory localizations in the *x* (mediolateral, with positive values for right hemisphere and negative values for left hemisphere), *y* (rostrocaudal, with negative values for caudal), and *z* (dorsoventral, with positive values for dorsal) axes in the MNI space. Individual and group activations were significant at $p < 0.001$ without correction or $p < 0.05$ with FWE correction for multiple comparisons. –, no functional activations detected.

estimated cortical thickness of the individual genital representation field (for individual data, see Table 2). Partial correlation analysis controlling for age, years since onset of sexual contract, and whole-brain cortical thickness revealed a significant positive correlation between cortical thickness of the individually-mapped left-hemispheric genital field and the frequency of sexual intercourse within the past 12 months ($r = 0.701$, $p = 0.004$; corrected $p < 0.05$). Similarly, longer-term frequency of sexual intercourse estimated since the onset of sexual contact was significantly correlated with thickness of the individually-mapped left-hemispheric genital field in a partial correlation analysis ($r = 0.538$, $p = 0.039$). Partial correlation analyses between cortical thickness of the right-hemispheric genital field and frequency of sexual intercourse did not reveal any significant effects, suggesting lateralized use-associated structural variation. Figure 5 shows scatterplots of left genital field thickness against frequency of sexual intercourse for the past 12 months and frequency of sexual intercourse since the onset of sexual contact, plotted as residuals corrected for covariates. Of note, menstrual cycle phase was not significantly associated with thickness of the genital field.

To confirm the specificity of this effect, we mapped individual ROIs for the representation of the hand (representing the 10 most activated vertices in the left hemisphere in response to stimulation of the right hand) onto native cortical surfaces for each woman and estimated cortical thickness of the individual representation field of the hand (for individual data, see Table 2). Importantly, cortical thickness of the hand representation was not significantly associated with frequency of sexual intercourse at either time window, with or without correction for the effects of covariates, reflecting a highly specific use-dependent effect for the sensory field involved in the specific behavior.

Discussion

We present novel evidence on the precise location of the female genital representation field and its capacity for use-associated structural variation. Using functional mapping during sensory-tactile stimulation of the clitoral region, we show focal bilateral neural activations within the dorsolateral postcentral gyrus in S1. We show that the individual location of peak neural activations in response to clitoral stimulation varies considerably between women. We applied cortical surface analysis to the individually-mapped ROI to compute structural thickness of the genital field. Correlating the individually-mapped morphologic data with behavioral data on sexual contact, we provide first evidence that thickness of the genital field varies as a function of frequency of genital intercourse in the past 12 months and lifetime, in line with use-associated plasticity.

Our results are noteworthy in several ways. To localize the female genital field, we measured neural response in a tactile-sensory stimulation paradigm that delivers a physiologically valid stimulus as opposed to a previous study using electrical stimulation of the clitoris (Michels et al., 2010). Furthermore, our tactile-sensory stimulation paradigm did not involve touching of body parts adjacent to the clitoris nor did it induce marked sexual arousal as opposed to previous studies using self-delivered or partner-delivered stimulation (Georgiadis et al., 2006, 2009, 2010; Komisaruk et al., 2011). The sole other study that used a sensory-tactile nonarousing stimulation paradigm to localize the genital field was limited to males (Kell et al., 2005). Our stimulation paradigm induced focal targeted neural activations, without inducing neural activation in other brain regions, at comparatively (Kell et al., 2005; Michels et al., 2010) high levels of statistical significance without using somatosensory template masks. Therefore, our data provide unequivocal information about the location of the female genital field and represent a significant methodological advance compared with previous studies that

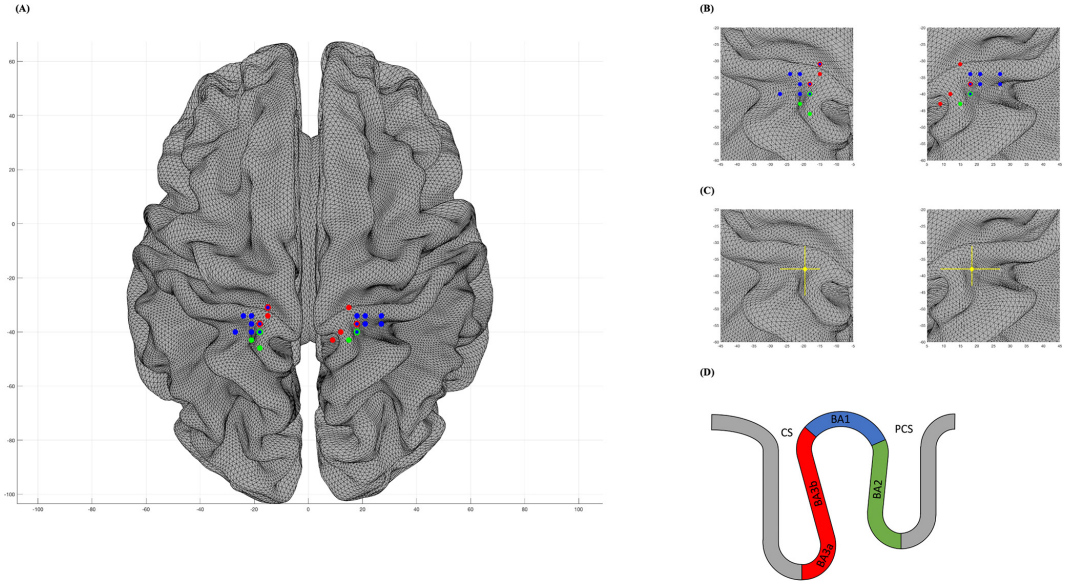

Figure 2. Interindividual variability of the genital somatosensory cortex in the MNI space. ***A***, Bilateral distribution of single subjects' representation of the clitoris in S1. Brodmann classification was based on probabilistic cytoarchitectonic maps (JuBrain Anatomy Toolbox v3.0; Simon Eickhoff, Institut für Neurowissenschaften und Medizin, Forschungszentrum Jülich, Jülich, Germany). Bicolored data points indicate overlapping Brodmann areas, depending on the *z*-coordinate in the transverse plane (see ***D***). ***B***, Detailed distribution over the two hemispheres, respectively. ***C***, Barycentres of the genital representations (shown in dots) on the left and right hemisphere with amplitude bars representing the dispersion (shown in lines). MNI barycentres of the genital representation on the left hemisphere [$x = -19.5$ (SE: ± 2.8, range: -27 to -15), $y = -38$ (SE: ± 3.6, range: -46 to -31), $z = 72$ (SE: ± 4.3, range: 62–80)] and right hemisphere [$x = 18.5$ (SE: ± 4.3, range: 9 to 27), $y = -38$ (SE: ± 2.8, range: -43 to -31), $z = 71.5$ (SE: ± 4.3, range: 62–80)]. ***D***, Schematic representation of the anterior parietal areas BA3a, BA3b, BA1, and BA2, indicating that all data points lay within the postcentral gyrus based on a probabilistic atlas of human cortical brain areas (Harvard–Oxford macroanatomical atlas).

yielded conflicting results (Georgiadis et al., 2006, 2009; Michels et al., 2010; Komisaruk et al., 2011), likely because of confounding factors inherent to stimulation paradigms used in these studies (Pratt et al., 1980; Forss et al., 1994). On a group level, the mean location of the female genital field in the dorsolateral postcentral gyrus, identified in our study, corresponds with the location reported in two of the previous studies in females using electrical (Michels et al., 2010) or partner-delivered manual stimulation (Georgiadis et al., 2006) as well as with the location reported for males in the above-referenced study using sensory-tactile stimulation in males (Kell et al., 2005). Our results confirm a somatotopically-ordered representation of the female clitoris, adjacent to the representation of the hips and upper legs and commensurate with anatomic location, and disprove displaced location in the mesial wall of the precentral lobe. Our results provide independent confirmation for the revision (Kell et al., 2005) of the original homunculus (Penfield and Rasmussen, 1950) and extend the validity of the revised homunculus to women. Our results confirm a bilateral somatosensory representation of the anatomically centered clitoris, in line with histologic mapping data on the localization and bilateral representation of the rat genital cortex (Lenschow et al., 2016; Lauer et al., 2017; Lenschow and Brecht, 2018).

Our results suggest profound variability of the individual location of the genital field within the dorsolateral part of S1 with individual peak activations clearly deviating from the group mean. This means that any study looking at structural variation of the genital field as a function of certain conditions, such as sexual behavior, sexual abuse or sexual dysfunction, must necessarily implement individual mapping of the genital field and compute data, i.e., cortical thickness, on an individual level. Clearly, only by using individually-mapped ROIs, such studies yield precise reliable surface-based parameters for association with specific conditions.

We computed data on structural thickness of the genital field in individually-mapped ROIs, based on the 10 most activated vertices per hemisphere for each woman. We show that individual thickness of the left genital field associates with frequency of sexual intercourse. The association was stronger for genital intercourse within the past 12 months. While less pronounced, the association was significant for lifetime genital contact. Frequency of genital intercourse was not associated with thickness of the representation field of the right hand nor with thickness of the entire cortical mantle, confirming a specific association between genital touch and genital field thickness. This is compatible with the idea that the female genital field has capacity for structural plasticity depending on its use, commensurate with the general "use-it-or-lose-it" principle of experience-dependent plasticity (Hebb, 1947; Elbert and Rockstroh, 2004; Draganski and May, 2008). While injury-dependent or use-dependent plasticity in the human somatosensory cortex has been reported (Elbert et al., 1994, 1995; Flor et al., 1995; Foell et al., 2014), our results are the first to document structural variation of genital field thickness associated with more or less frequent normative use. Our results are in line with findings from animal studies showing that genital brushing during puberty resulted in lateral expansion of the rat and mouse genital cortex (Lenschow et al., 2017; Sigl-Glöckner et al., 2019). Cortical plasticity serves to enhance the efficiency of processing of behaviorally-relevant inputs and represents an adaptive response (Trachtenberg et al., 2002; Markham and

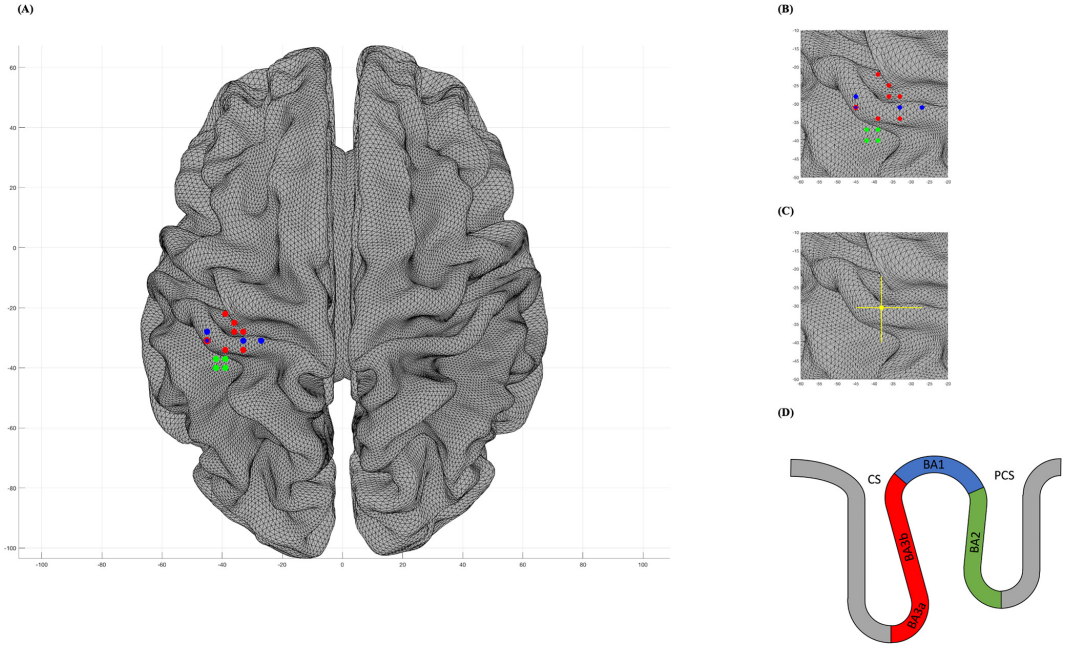

Figure 3. Interindividual variability of the hand somatosensory representation in the MNI space. ***A***, Contralateral distribution of single subjects' representation of the right dorsum of the hand in S1. Brodmann classification was based on probabilistic cytoarchitectonic maps (JuBrain Anatomy Toolbox v3.0; Simon Eickhoff, Institut für Neurowissenschaften und Medizin, Forschungszentrum Jülich, Jülich, Germany). Bicolored data points indicate overlapping Brodmann areas, depending on the *z*-coordinate in the transverse plane (see ***D***). ***B***, Detailed distribution over the left hemisphere. ***C***, Barycentre of the hand representation (shown in dots) on the left hemisphere with amplitude bars representing the dispersion (shown in lines). MNI barycentres of the hand representation on the left hemisphere [$x = -38$ (SE: ± 4.3, range: -45 to -27), $y = -30.5$ (SE: ± 4.3, range: -40 to -22), $z = 62$ (SE: ± 5.0, range: 53–74)]. ***D***, Schematic representation of the anterior parietal areas BA3a, BA3b, BA1, and BA2, indicating that all data points lay within the postcentral gyrus based on a probabilistic atlas of human cortical brain areas (Harvard–Oxford macroanatomical atlas).

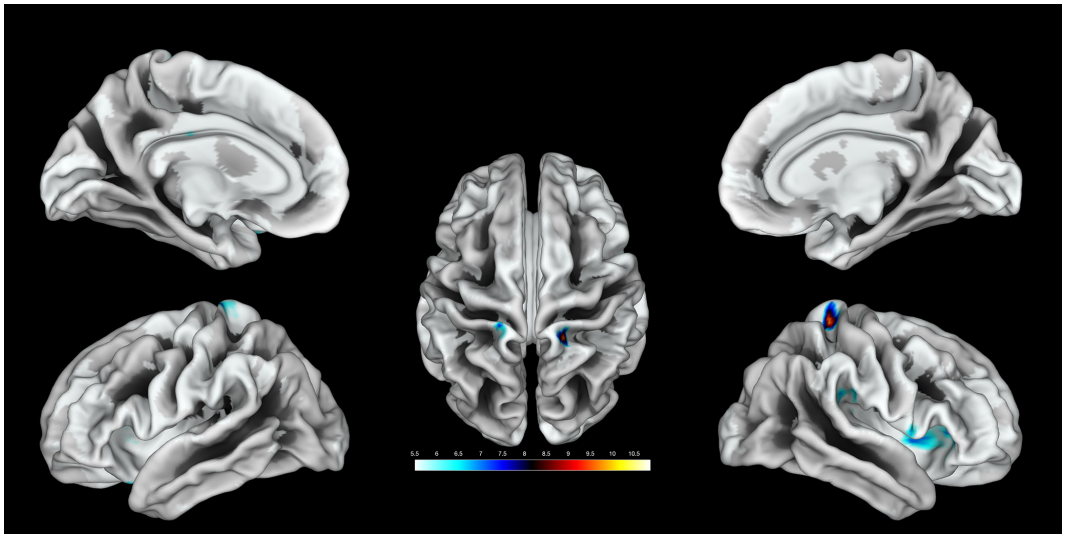

Figure 4. Cortical surface mapping of functional somatosensory activations of the random effects GLMs of sensory-tactile stimulation of the clitoral region (left hemisphere: $x = -18$, $y = -34$, $z = 74$; $T = 7.72$, $p_{FWE\text{-}corr} = 0.024$; right hemisphere: $x = 18$, $y = -40$, $z = 68$; $T = 10.26$, $p_{FWE\text{-}corr} < 0.0001$).

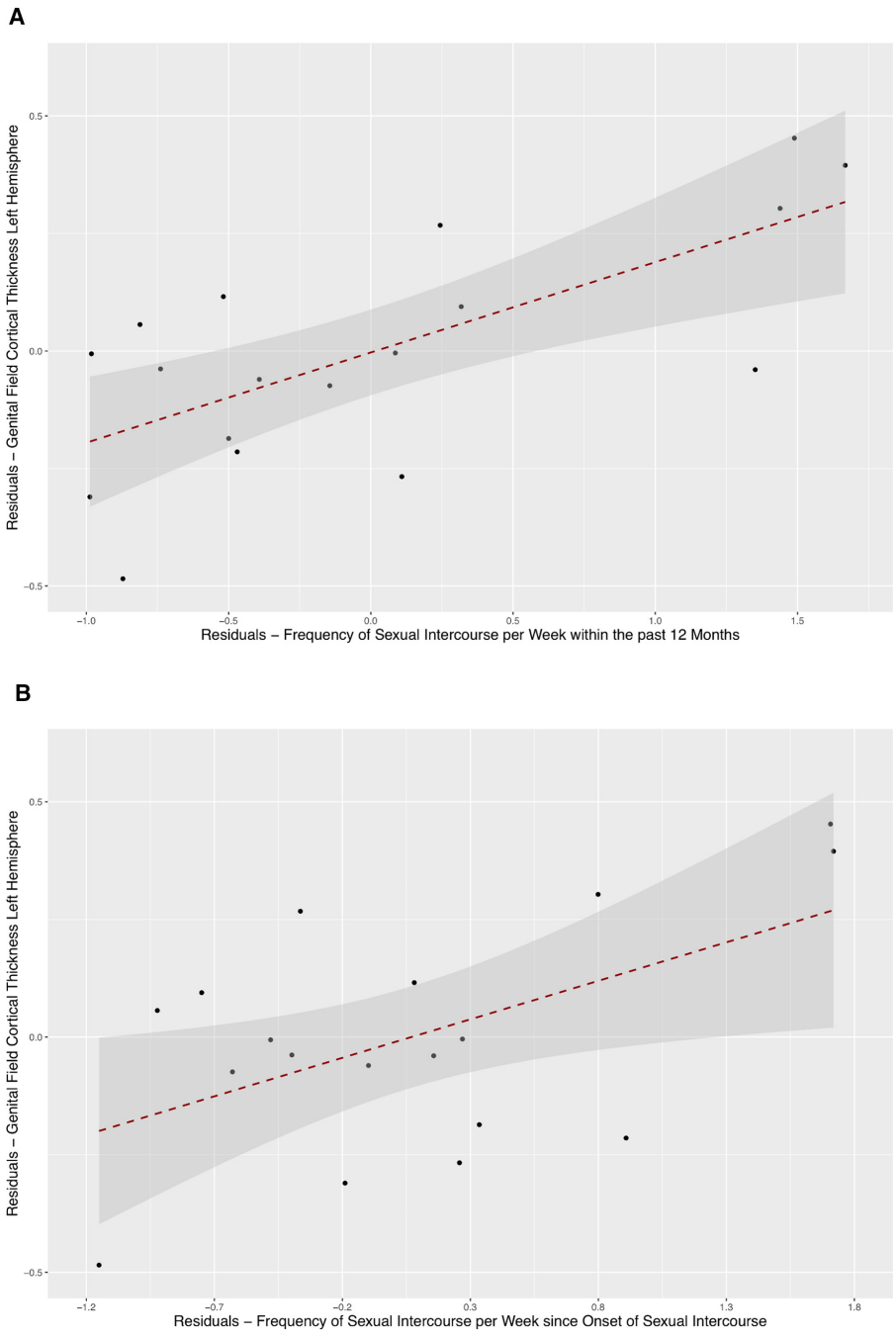

Figure 5. ***A***, Scatter plot with SE on the correlation between frequency of sexual intercourse per week within the past 12 months and left-hemispheric genital field cortical thickness. Data points are plotted as residuals with correction for covariates. ***B***, Scatter plot with SE on the correlation between frequency of sexual intercourse per week since onset of sexual contact and left-hemispheric genital field cortical thickness. Data points are plotted as residuals with correction for covariates. (Partial correlation values of covariates with genital field cortical thickness: age: $r = -0.460$, $p = 0.055$; years of sexual intercourse: $r = -0.380$, $p = 0.120$; whole-brain cortical thickness: $r = 0.309$, $p = 0.213$.)

Greenough, 2004; Feldman and Brecht, 2005; May, 2011). In an earlier study, we observed decreased thickness of the genital cortex after exposure to childhood sexual abuse, suggesting that highly aversive and developmentally inappropriate sexual stimulation may limit somatosensory representation to decrease processing of detrimental input (Heim et al., 2013).

Several mechanisms might contribute to dynamic use-associated structural plasticity of the genital field. Structural thickening of the mature cortex as a function of use most likely reflects formation of new synapses by axonal sprouting, dendritic arborization, and dendritic spine growth rather than induction of new neurons through neurogenesis (Markham and Greenough, 2004; Feldman and Brecht, 2005; Feldman, 2009; May, 2011). There is substantial evidence on the central role of glutamatergic synapses in mediating plasticity, reflecting rapid components of NMDA receptor-dependent long-term potentiation (LTP) and long-term depression (LTD; Buonomano and Merzenich, 1998; Feldman, 2009). Another mechanism contributing to use-associated structural plasticity may involve alterations in glial-cell mediated myelination (Timmler and Simons, 2019). While oligodendrogenesis is rare (Yeung et al., 2019), the presence of large numbers of premyelinating oligodendrocytes in the human cortex may enable adaptive myelination to adapt conduction velocity to functional demand (Gibson et al., 2014). Future studies in humans should use novel imaging tools that allow for assessing cortical myelin density (Amunts and Zilles, 2015) to study genital field plasticity. Further, neural activation in response to somatosensory stimulation depends on axonal input from the thalamus (Feldman, 2009). When removing afferent somatosensory input from the thalamus, dendritic spine numbers of somatosensory cortical neurons attenuate (Lendvai et al., 2000). When exposing rats to genital touch or sexual contact during puberty, invading thalamo-cortical afferents promote the expansion of the female genital cortex (Lenschow et al., 2016). Future studies on genital field plasticity should therefore include assessments of thalamo-cortical connectivity and myelination.

It must be noted that use-associated variation of structural thickness of the female genital field in our study was limited to the left hemisphere. This lateralized effect is puzzling given that the neural representation of the clitoris is bilateral. Left-hemispheric dominance of neural plasticity has been reported for learning-dependent structural change after coordination and motor skill training (Draganski et al., 2004; Taubert et al., 2010; Rogge et al., 2018). Such lateralized plasticity may reflect hemispheric specialization (Serrien et al., 2006). In the above referenced study (Heim et al., 2013), thinning of the genital field after sexual abuse was limited to the left hemisphere. While we cannot comprehensively explain these findings, one plausible mechanism may involve lateralized limbic-cortical modulation of sensory afferent inputs into the genital field, leading to unilateral associations of sexual behavior with genital field morphology.

While our localization of the female genital field was experimental in nature, our investigation of the capacity of the genital field for structural variation as a function of genital contact was cross-sectional and relied on retrospective self-report of genital intercourse. Our results align with the general principle of an association between frequency of genital intercourse and structural variation, albeit the direction of effect is a matter of discussion. It is conceivable that thickness of the genital field may drive frequency of sexual intercourse. Results from animal models provide causal that clitoral stimulation drives genital field thickness (Lenschow et al., 2016; Lenschow and Brecht, 2018). Future prospective studies or studies exploiting quasi-experimental conditions, such as induction of behavior change during sexual therapy, are needed to establish causality.

In conclusion, we provide an unequivocal localization of the female genital field in S1 and support for use-associated plasticity of the human genital field. On a secondary level, our findings support the notion that studies investigating change of the human genital field must map the field individually. Our results pave the way for future research into the plasticity of the human genital field as a function of normal or adverse experience as well as genital field structure, function and plasticity in pathologic conditions, such sexual dysfunction, sexual deviation, or sexual risk-taking behavior.

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Curriculum Vitae

My curriculum vitae does not appear in the electronic version of my paper for reasons of data protection.

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