GENITAL STIMULATION, IMAGERY, AND ORGASM IN WOMEN: AN FMRI ANALYSIS

by

NAN WISE

A Doctoral Dissertation submitted to the Graduate School - Newark

Rutgers, The State University of New Jersey

in partial fulfillment of the requirements for the degree of

Doctor of Philosophy

Graduate Program in Psychology

written under the direction of Barry R. Komisaruk, Ph.D.

_____

and approved by

Mauricio Delgado, Ph.D.

_____

Elizabeth Tricomi, Ph.D.

_____

Catherine Hanson, Ph.D.

_____

Beverly Whipple, Ph.D.

_____

Newark, New Jersey

October, 2014

ABSTRACT OF THE DISSERTATION

Genital stimulation, imagery, and orgasm in women: An fMRI analysis

By Nan Wise

Dissertation Director
Barry R. Komisaruk, Ph.D.

The main questions addressed in my dissertation are: 1) how does fMRI-measured activity of the brain respond to physical versus imagined stimulation of the genitals, and 2) as the brain activity progresses from response to genital stimulation through orgasm to its resolution, how does the regional activity change?

These questions are addressed in the form of two studies: 1) Activation of sensory and other brain regions in response to imagined versus physical genital stimulation, and 2) Brain regional activation upon transition to self- and partner-induced orgasm in women. The first study developed from a genital sensory mapping study (Komisaruk, Wise et al, 2011) in which our control condition revealed the intriguing serendipitous finding that just *imagining* genital or nipple stimulation activated the same regions of the genital sensory cortex as did actual tactile stimulation of these body regions. We extended this surprising finding by focusing on a comparison between *tactile* versus *imagined* stimulation of the nipple and clitoris. We designed two additional conditions -- imagined dildo stimulation versus imagined speculum stimulation -- to investigate possible

differences in erotic versus non-erotic imagery. The present findings provide evidence that imagery activates brain regions implicated in bodily sensation, orgasm, and reward, some of which overlap with, and others that are different from, the brain regions that respond to tactile self-stimulation, e.g., paracentral lobule (the “genital sensory cortex”) and the prefrontal cortex, respectively.

The second study addressed a major discrepancy in the literature regarding whether frontal and temporal cortical regions are activated (Komisaruk et al., 2004; 2005) or deactivated (Georgiadis et al., 2006; 2009) during orgasm. In addition to the different methods used (fMRI versus PET, respectively), a major procedural difference was that genital *self*-stimulation was employed in our fMRI studies while genital *partner-applied* stimulation was used in the PET studies. In an attempt to resolve the discrepancy, in the present study, we compared the regional brain activity observed during *self*- versus the *partner*-induced orgasm conditions. We found no deactivation of frontal or temporal regions during self- or partner stimulation-induced orgasm. Neither were there significant regional differences in activity between the self- and partner stimulation-induced orgasms. Consequently, we combined the data from the self-stimulation and partner-stimulation-induced orgasm groups. This analysis revealed widespread activation throughout the brain, including primary sensory, motor, sensory-motor integration and reward regions, whose distribution pattern changed in sequence, leading up to, during, and after orgasm.

[Please refer to Appendix H for defense presentation summary of both studies]

Dedication

To my husband, John, and my children, Adam and Julia

Your love and support gave me the courage to pursue my dreams

Acknowledgments

At the tender age of fifty, after twenty-five years of practice as a psychotherapist, I met Dr. Beverly Whipple at a sex therapy training program. Over lunch, she suggested I help with the research she was conducting with Dr. Barry Komisaruk (who, coincidentally, had been my professor at the Institute of Animal Behavior in the early 1980s). Within a few weeks, I was at the scanner facility with the team. Within a few months, I was enrolled in the doctoral program. First and foremost, I thank Beverly for opening the door, and Barry, for guiding me in. I have been extraordinarily fortunate to have these two powerhouse mentors nurture and support me every step of the way. Doing this work, with these people, has been a labor of love. My lab family is extraordinarily dear to me. Eleni Frangos, my lab daughter, has been my friend, my lab mate, and a wonderful midwife through the birth of this dissertation. Her work in helping me improve this document was invaluable. Wendy Birbano, my lab sister, has given me abundant hugs and incredible technical help. Beverly Whipple has become a dear friend and collaborator. And special thanks to Barry Komisaruk for being a trailblazer and visionary, taking us all on an incredible journey I could not have imagined, even in my wildest dreams. Without his encouragement, I would never have embarked on this adventure. I am indebted to so many kind souls for their stewardship. John Dell'Italia had the patience of a saint when faced with the daunting task of teaching me computer command line basics. Mauricio Delgado was especially welcoming when I took the first class, as a "provisional" student, and made cognitive neuroscience accessible and fun.

Kachina Allen showed up exactly when we needed her data expertise, and rapidly became part of the family. Eebie Tricomi's mere presence in the psychology department is a soothing balm. She is a great role model for all. And to Catherine Hanson, I am forever grateful to you, and your husband, Steve, for creating an fMRI methods course that was a veritable training playground. Catherine's patience, good humor, and encouragement were hugely helpful. Also, big thanks to Gene and Monica McGovern for exceptional love, companionship, and support throughout the years. And to my family of origin, I give thanks for passing on good genes and an insatiable curiosity. And last, but not least, to my husband, John, for having the courage to live this dream with me—and my children, Adam, and Julia, for filling my soul with joy every day.

Table of Contents

List of Tables

List of Figures

Experiment 2: Brain regional activation upon transition to self- and partner-induced orgasm in women: an fMRI analysis.

List of Appendices

ABSTRACT

Activation of sensory and other brain regions in response to imagined versus physical genital stimulation

Eleven healthy women (age range 29-74 years) participated in an fMRI study of how the brain processes tactile stimulation versus “imagined” stimulation of the nipple and clitoris. Two additional conditions -- imagined dildo self-stimulation versus imagined speculum stimulation -- were included to investigate possible differences in erotic versus non-erotic imagery. Imagined and physical self-stimulation of the nipple and clitoris both resulted in activation of the paracentral lobule (the genital sensory cortex) and the secondary somatosensory cortex. Imagined stimulation of clitoris and nipple resulted in greater activation of the frontal pole and orbital frontal cortex than did the actual tactile self-stimulation of these two bodily regions. Tactile self-stimulation resulted in greater activation of the cerebellum, primary somatosensory cortex (hand region), and motor cortex than did imagery. Imagining dildo self-stimulation generated extensive brain activation in the genital sensory cortex and “reward system”, whereas imagining speculum stimulation generated only minimal activation throughout the brain. The present findings provide evidence that imagery activates brain regions implicated in bodily sensation, orgasm, and reward that both overlap with, and are different from, the brain regions that respond to tactile self-stimulation.

1. Introduction

In a recent study (Komisaruk, Wise et al., 2011), we responded to the gap in the literature about the somatosensory representation of physical stimulation of the female genitals by systematically mapping the projections of the clitoris, vagina, cervix, and nipple onto the sensory cortex. We concluded that their representations were differentiable, but clustered, in the mesial paracentral lobule-- “the genital sensory cortex.” In the course of this study, a serendipitous finding arose from a control condition, during which the participants were instructed to “think” about self-stimulating their clitoris, vagina, and nipple: it was observed that just “imagining” stimulation of these regions generated activity in the genital sensory cortex that overlapped substantially with that induced by actual physical stimulation, although the imagery condition activations were of a lesser magnitude. In addition, thinking about stimulating a body part appeared to activate the dorsolateral prefrontal cortex, frontal superior medial cortex, and frontal inferior orbital cortex substantially more than did the corresponding physical stimulation (Wise et al., 2010).

These findings are consistent with recent studies demonstrating that imagery of stimulation of specific body regions activates corresponding regions of the primary, secondary somatosensory cortices (S1, S2) and the insula, although to a lesser degree than tactile stimulation of those body regions, while in contrast, the magnitude of activation of the inferior parietal lobule, medial frontal gyrus, dorsolateral prefrontal areas, and inferior frontal gyrus is greater for the tactile imagery conditions (Yoo et al., 2003; Olivetti Belardinelli et al., 2009).

The present study extends our serendipitous finding into an investigation of how the brain differentially processes physical “touch” stimulation and mental “imagined” stimulation of the nipple and clitoris. The reason that the clitoris was chosen for inclusion is that more studies have been done of the clitoris than other female genital regions, making it more pertinent to the replication of our previous findings and resolution of discrepancies in the literature [please refer to Appendix A: Somatosensory representation of female genitals, breast, and nipple]. The decision to include the nipple condition is based on our recent unexpected finding that stimulation of this region activates the genital sensory cortex (Komisaruk, Wise et al., 2011).

The present study extends the analysis of responsive brain regions to a systematic investigation of the secondary somatosensory cortex (S2) (see Appendix B: The secondary somatosensory cortex). In contrast to the primary somatosensory cortex, S2 is believed to participate in aspects of somatosensory attention (Chen et al., 2008), experimentally induced pain in women suffering from vulvar vestibulitis syndrome (Pukall et al., 2005), and, most relevant for the purpose of this study, the interpretation of sensation as erotic. Georgiadis et al., (2006) using PET, reported that the strongest activation during the clitoral stimulation condition, which participants described as erotically pleasurable, occurred in left S2, suggesting that it plays a role in the appraisal of tactile genital stimulation as erotic.

We hypothesized that for the imagery conditions there would be activations under these conditions observed in region S2 as well as in S1, most

likely in the medial portion of the operculum (area OP4), near the region of foot and anus representation (Young et al., 2004; Eickhoff et al., 2006a). We also hypothesized that the physical stimulation condition would result in greater activation of the primary somatosensory hand region, motor cortex, and cerebellum than the tactile imagery condition.

For the tactile imagery condition, we also hypothesized that the clitoral and nipple “imagine stimulate” conditions would activate corresponding regions of the mesial paracentral lobule--genital sensory cortex --and area OP4 of region S2, although to a lesser magnitude than the physical stimulation. Conversely, the tactile imagery condition was predicted to result in greater activation of the inferior frontal gyrus (BA 44), precentral/medial frontal gyrus (BA 6) and dorsolateral prefrontal cortex (BA 9/46).

Two additional imagery conditions -- imagined speculum and dildo stimulation-- were added to the study to explore the differences between imagery that has a prosaic versus erotic context. We expected that there would be significant differences between the “imagine speculum” and “imagine dildo” conditions, with the latter condition associated with the activation of the genital sensory cortex and other regions previously implicated in the processing of bodily sensation, sexual stimulation, and orgasm (Komisaruk et al., 2004, 2005). We anticipated that the participants would rate the dildo imagery condition more sexually arousing than the speculum imagery, although it would not be experienced as more vivid. To rule out that the differences between dildo and speculum imagery would not be the result of a negative valence of imagined

speculum stimulation, we collected data regarding whether the participants found any of the imagined stimulation conditions aversive.

1.1. Methods

1.1.1. Research participants

Thirteen healthy women (age range 29-74 years, M = 43.6, SD =13.6 years) were recruited for this study by word of mouth. Two of the participants had to be excluded from the study because one had excessive head movement during the scan and one participant's data was corrupted due to mismatched fields-of-view for functional and anatomical data at acquisition. Seven of the women reported being in a significant relationship; five stated that they have children. The participants each gave informed consent per the Rutgers University Institutional Review Board for this approved study. Each participant also granted the investigator the optional permission to use her interview statements anonymously for presentations and publications. The scanning session took place at the Rutgers University Brain Imaging Center (RUBIC, Newark, NJ), in compliance with all RUBIC MRI common practices. The participants were prescreened for MRI safety and complete screening forms per RUBIC requirements, including the pregnancy release form. Each participant completed two open-ended interviews conducted by the author [please refer to Appendix C for interview questions]. The pre-scan interview included questions about the participant's sexual and relationship histories, influences, attitudes about

sexuality, current sexual behaviors, and preferences regarding sexuality. This information will not be analyzed for this manuscript. All participants were debriefed in a post-scan interview, during which information about their experience in the scanner was collected. The participants were asked to rate the vividness of their imagery experiences during the various imagery conditions on a scale of 1 (no image/sensation) to 7 (very vivid image/sensation). They were also asked to rate how sexually aroused they were from 1 (low) to 7 (high) during each of the physical stimulation and imagined stimulation conditions. Prior to the scanning session, each participant reviewed the scheduled protocol for practice such that she was familiar with the different physical and imagery tasks she was asked to do during the experiment. Participants were paid $50 for their participation in the study.

1.1.2. Experimental paradigm

Experiment 1 comprised approximately the first 22 minutes of the scanning procedure. After acquisition of localizers and MPRAGE anatomical images (see FMRI acquisition and data analysis section), the participants followed instructions presented visually on an fMRI-compatible screen. For the first 60 seconds the participants were instructed to rest. The experimental protocol consisted of four five-minute trials in the following order: Nipple Imagine Stimulation (NIS), Clitoris Imagine Stimulation (CIS), Nipple Touch Stimulation (NTS), and Clitoris Touch Stimulation (CTS). Each trial consisted of 30s of “modeling” of either the physical or imagined stimulation followed by 30s

of engaging in either mental imagery or physical stimulation “to comfortable intensity” as instructed, repeating 5 times in succession for a total of five minutes.

To make the “model” condition clear, consider the Nipple Touch Stimulation trial. The participant first sees the instruction displayed on the screen, “nipple model,” which cues her to make the hand movements that she would do to rhythmically stimulate her nipple without actually touching herself. Thus, the participant moved the fingers of her right hand above her left nipple, fingers touching each other but not her nipple, for 30s. This alternated with 30 s of actual nipple “touch,” during which the participant was cued to use her right hand to rhythmically stimulate her left nipple. This sequence of nipple “model” and nipple “touch” alternated five successive times for a total of five minutes.

Similarly, during the Clitoris Touch Stimulation trial, the participant first saw the instruction displayed on the screen, “clitoris model,” which cued her to make the hand movements that she would do to rhythmically stimulate her clitoris without actually touching herself. Thus, the participant moved the fingers of her right hand above her clitoris, fingers touching each other but not her clitoris, for 30 s. This alternated with 30 s of actual clitoris “touch,” during which the participant was cued to use her right hand to rhythmically stimulate her clitoris. This sequence of clitoris “model” and clitoris “touch” alternated five successive times for a total of five minutes.

For the imagery trials, the “model” condition was analogous to the model condition for the physical trials, but the participant was instructed to *think* about making the modeling movements rather than actually execute them. For example, during the Nipple Imagine Stimulation trial, the participant was first instructed to “think model,” which cues her to think about making rhythmic movements with her left hand over her right nipple for 30s. Then she saw the instruction, “think nipple stimulate,” which cued her to *imagine* rhythmically touching her left nipple with her right hand for 30 s. This sequence repeated five times for a total of five minutes.

The Clitoris Imagine Stimulation trial, likewise, alternated 30 s of imagined right hand “model” movements with 30s of imagined stimulation of the clitoris for a total of 5 minutes.

The protocol sequence began with the imagery trials to avoid the potential priming effects that actual physical stimulation could induce. The physical trials started with nipple rather than clitoris stimulation to avoid the potential confound of any lingering effects from stimulation of the clitoris. Because of these concerns, the conditions were not be counterbalanced and the trials were always presented in the following order: Nipple Imagine Stimulation, Clitoris Imagine Stimulation, Nipple Touch Stimulation, and Clitoris Touch Stimulation.

Following completion of the imagery and physical stimulation trials, after a brief rest, Experiment 1 concluded with an additional imagery sequence during which the participant viewed instructions to “imagine speculum” (to think

about having a speculum inserted into her vagina by another person) for 30s, followed by instructions to “imagine dildo” (to think about having a dildo inserted into her vagina by another person) for 60s, and ending with another trial of “imagine speculum” for the final 30 seconds.

1.1.3. fMRI acquisition and data analysis

The fMRI scans were performed at the Rutgers University Brain Imaging Center using a 3T Siemens Trio with a Siemens 12-channel head coil. For registration purposes, anatomical images were acquired using magnetization prepared rapid gradient echo (MPRAGE) sequences (176 slices in the sagittal plane using 1mm thick isotropic voxels, TR/TE = 1900/2.52ms, field of view = 256, 256 x 256 matrix, flip angle = 9 degrees; 50% distance factor). Gradient-echo EPI sequences were acquired of the whole brain including the entire medulla oblongata (33 slices in the axial plane using 3mm isotropic voxels, TR/TE = 2000ms/30ms, interslice gap = 1.5 mm, flip angle = 90, field of view = 192, 64x64).

All data were preprocessed and statistically analyzed using FMRIB’s (Center for Functional Magnetic Resonance Imaging of the Brain, University of Oxford, UK) Software Library (FSL) version 6.00. Lower-level fMRI data processing was carried out using FMRI Expert Analysis Tool (FEAT).

Each participant’s functional data were split into three files using FSLUTILS (fslroi) to create three separate data sets for analysis: (a) the physical stimulation/imagined stimulation conditions for use in Experiment 1: Activation of

sensory and other brain regions in response to imagined versus physical genital stimulation; (b), the genital self-stimulation-induced orgasm condition, and (c), and the partner-stimulation-induced condition to be analyzed for Experiment 2: Brain regional activation upon transition to self- and partner-induced orgasm in women: an fMRI analysis

Separate pre-processing and statistical analyses were performed for each data set. The following pre-processing steps were performed at the individual level: manual removal of skull and non-brain tissue from the anatomical and functional images.

For the analysis of the physical stimulation/imagined stimulation data, MCFLIRT (Jenkinson et al., 2002) motion correction was performed with extended motion parameters added to the model. The average mean motion displacement movement for these data were absolute = .3730 mm, relative = .1007 mm. All data were spatially smoothed using a 5mm full-width at half-maximum Gaussian kernel. Registration of the functional images to the high-resolution anatomical images was performed outside of the FEAT, using FLIRT (FMRIB's Linear Image Registration Tool), selecting the options: Mutual Information Cost Function and Sinc Interpolation (Blackman, width of Sinc Window= 7 voxels). Each participant's first level FEAT registration file was updated with the FLIRT registration conducted outside of FEAT prior to the higher-level analyses.

Explanatory variables (EVs) were created at the first levels for Nipple Imagine Model (NIM), Nipple Imagine Stimulation (NIS), Clitoris Imagine Model

(CIM), Clitoris Imagine Stimulate (CIS), Nipple Touch Model (NTM), Nipple Touch (NTS), Clitoris Touch Model (CTM), Clitoris Touch Stimulate (CTS), Imagine Speculum (IS), and Imagine Dildo (ID). First level basic contrasts were set up for all EVs > 0 and < 0 (0 = global baseline). Differential contrasts were also set up to compare each "stimulation" condition (stimulate) with its "control" condition (model): NIS>NIM, CIS>CIM, NTS>NTM, and CTS>CTM. Additional differential contrasts comparing across imagined stimulation and physical stimulation conditions were also set up: NIS>NTS; NTS>NIS; CIS>CTS; CTS>CIS. Contrasts were also set up to compare the two additional imagery conditions, ID>IS and IS>ID.

First level analyses were conducted with a high pass filter cutoff set at 180 s. FILM (FMRIB's Improved Linear Model) prewhitening option was selected to improve estimation efficiency. The data were convolved using a double-gamma HRF without temporal derivatives. The EVs were used as regressors to determine the average activity elicited by each condition. The data at first levels were corrected for multiple comparisons using a cluster-forming threshold of z=1.65 and a cluster-significance threshold of p = 0.05. The output files (contrast of parameter estimates, or "cope" files) were then used in the higher-level analysis to determine mean group effects and to perform contrast analyses between the conditions.

Higher-level analyses were performed using FMRIB's Local Analysis of Mixed Effects (FLAME 1). To explore the data, a whole brain group analysis was conducted using a cluster-forming threshold of z = 1.65 and a cluster-significance

threshold of $p < 0.05$. As the activity of the imagined stimulation differential contrasts (CIS>CIM; NIS>NIM) was significantly and unexpectedly greater than the activity observed in the physical stimulation differential contrasts (NTS>NTM; CTS>CTM), it was determined that the results of the differential contrasts for the subsequent group analyses for this data set should be contrast-masked post-threshold with the constituent basic contrast conditions greater than baseline to assure that the activity observed in the differential contrasts was positively driven. For example, the differential contrast CIS>CIM was contrast-masked with the positive voxels of each of the basic contrasts, specifically CIS>0 and CIM>0 (greater than global baseline) assuring that the results of all differential contrasts reflect only activity above the global baseline. This was done for all differential contrasts.

To further improve the power of the higher-level analyses, a region of interest analysis was also conducted for the group data. Based on pilot data (Wise et al, 2010) and a review of the literature, masks for the following regions of interest (ROIs) were generated using Harvard-Oxford Cortical and Subcortical Structural Atlases and the Juelich Histological Atlas: postcentral gyrus, parietal operculum regions 1-4, frontal lobe, hippocampus, insula, nucleus accumbens, thalamus, and cerebellum. A mask for the paracentral lobule of the cerebral cortex was created manually.

All higher-level analyses of this data set were corrected for multiple comparisons and contrast-masked post-threshold with the voxels above baseline as described. For the contrasts involving the physical and imagined stimulation of

the nipple and clitoris, the cluster-forming z was set at 1.0, cluster-significance threshold p= 0.01. For the contrasts comparing the imagery of the dildo (ID) and the speculum (IS) the cluster-forming threshold was set at z = 1.65, p=0.05.

1.2. Results [Please refer to Appendix H for summary of results]

1.2.1. Physical versus imagined stimulation of the clitoris and nipple

Regions that were activated by both physical and imagined stimulation of clitoris or nipple included the mesial paracentral lobule, secondary somatosensory cortex (parietal operculum), cerebellum, and frontal cortex.

The imagery condition resulted in greater activity of the frontal pole and orbital frontal cortex than did the physical stimulation condition; the physical stimulation condition resulted in greater activation of the cerebellum, primary somatosensory cortex (hand region), parietal operculum (OP1 right), and motor cortex than did the imagery condition.

Regions that were activated only during the imagined stimulation condition include the insular cortex, amygdala, hippocampus, and inferior parietal lobule.

A) Paracentral lobule

The mesial paracentral lobule was activated by both physical (Figure 1) and imagined (Figure 2) stimulation of the clitoris and nipple. There was no significant difference between physical and imagined stimulation for these conditions. There was significantly more activation in the paracentral lobule for

the imagined stimulation of the clitoris than imagined stimulation of the nipple (Figure 3).

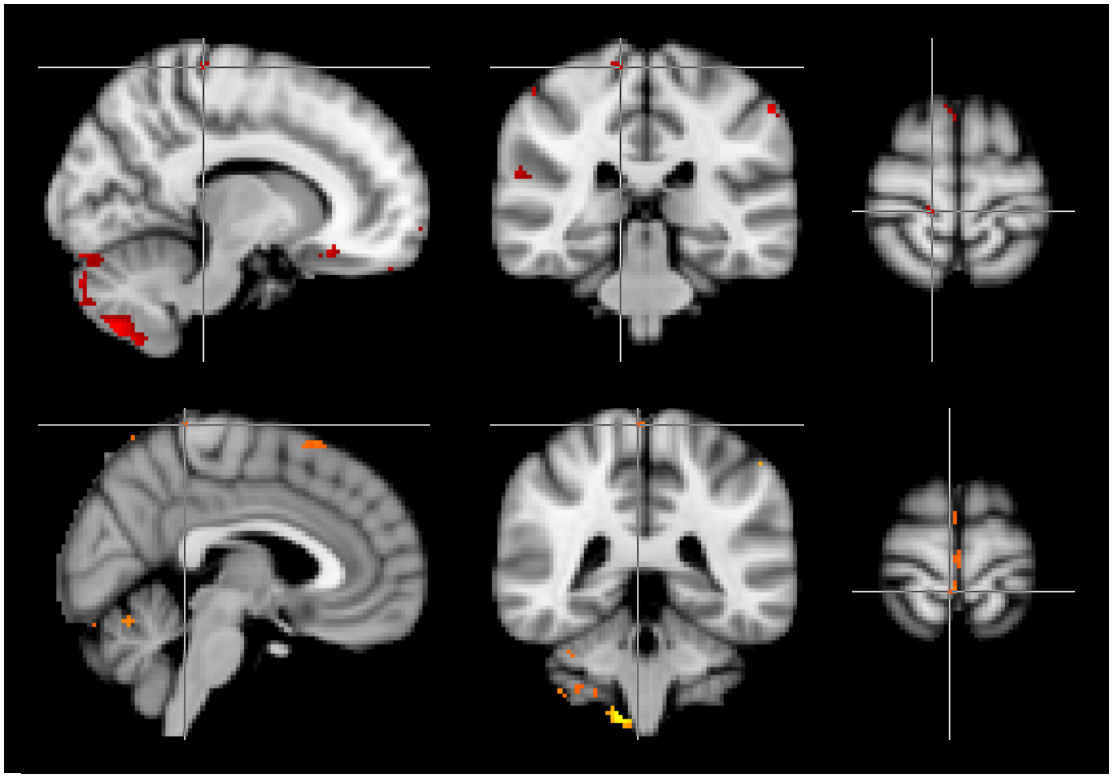


Figure 1. Mesial paracentral lobule activated by physical stimulation of the clitoris (top) and nipple (bottom). Flame 1; cluster z =1.0, p <0.01.

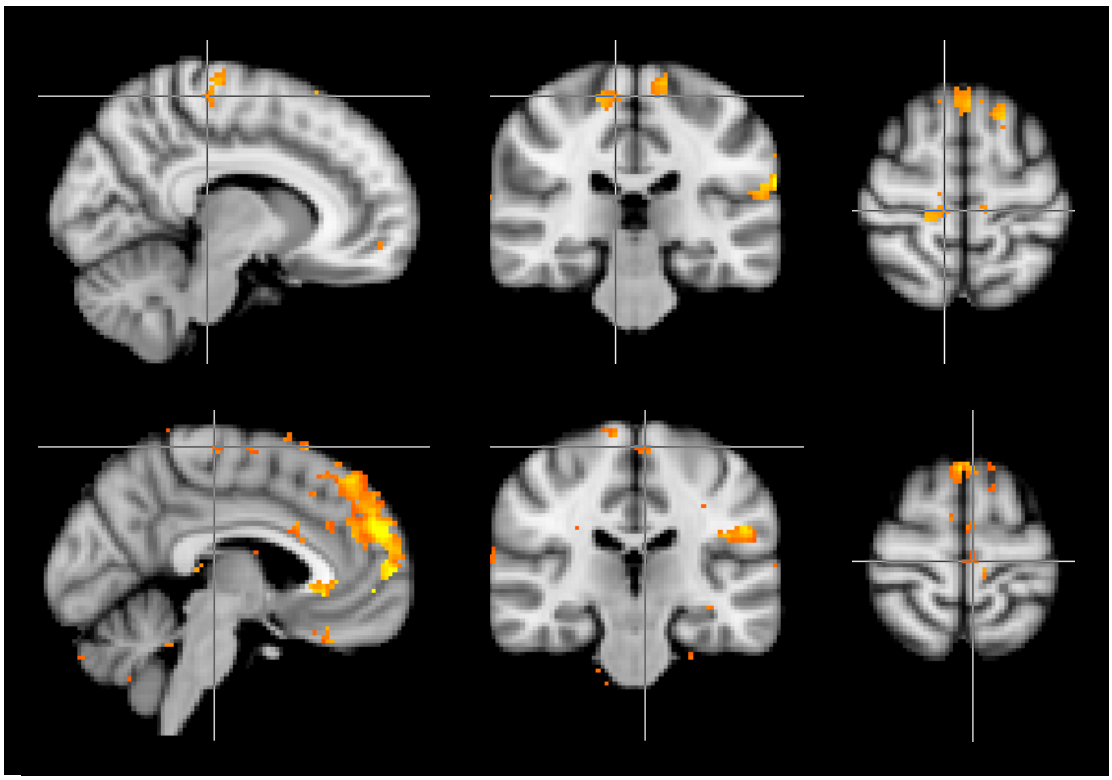


Figure 2. Mesial paracentral lobule activated by imagined stimulation of the clitoris (top) and nipple (bottom). Flame 1; cluster z =1.0, p <0.01.

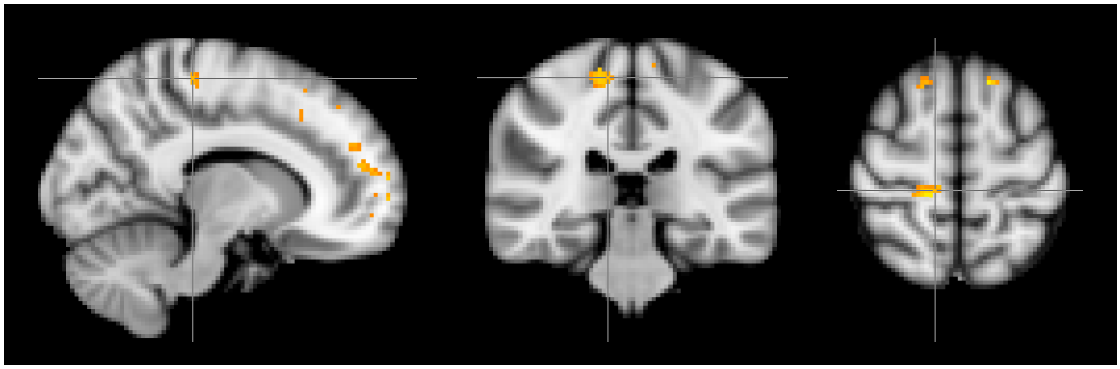


Figure 3: Mesial paracentral lobule activation greater for imagined stimulation of the clitoris (compared with imagined nipple stimulation). Flame 1; cluster z =1.0, p <0.01.

B) Frontal cortex

Small regions of activation of the frontal pole activation are noted in the clitoris physical stimulation condition, with less observed in the nipple physical stimulation condition (Figure 4).

For imagined stimulation of the clitoris, activations are observed in the orbital frontal cortex, frontal pole, frontal medial cortex, superior frontal gyrus, inferior frontal gyrus, dorsolateral prefrontal cortex, and anterior cingulate gyrus. A similar pattern, with less overall activity, is noted for nipple imagine stimulation (Figure 5). In general, there appeared to be more overall activity on the left side of the frontal regions [please refer to Appendix D for additional imagery results].

When the data were collapsed across conditions for imagery and physical stimulation (Figure 6) the resulting contrast indicated greater activity of the left orbital frontal cortex and frontal pole in the imagery condition.

There were no significant results for activity greater in the physical than the imagined stimulation conditions.

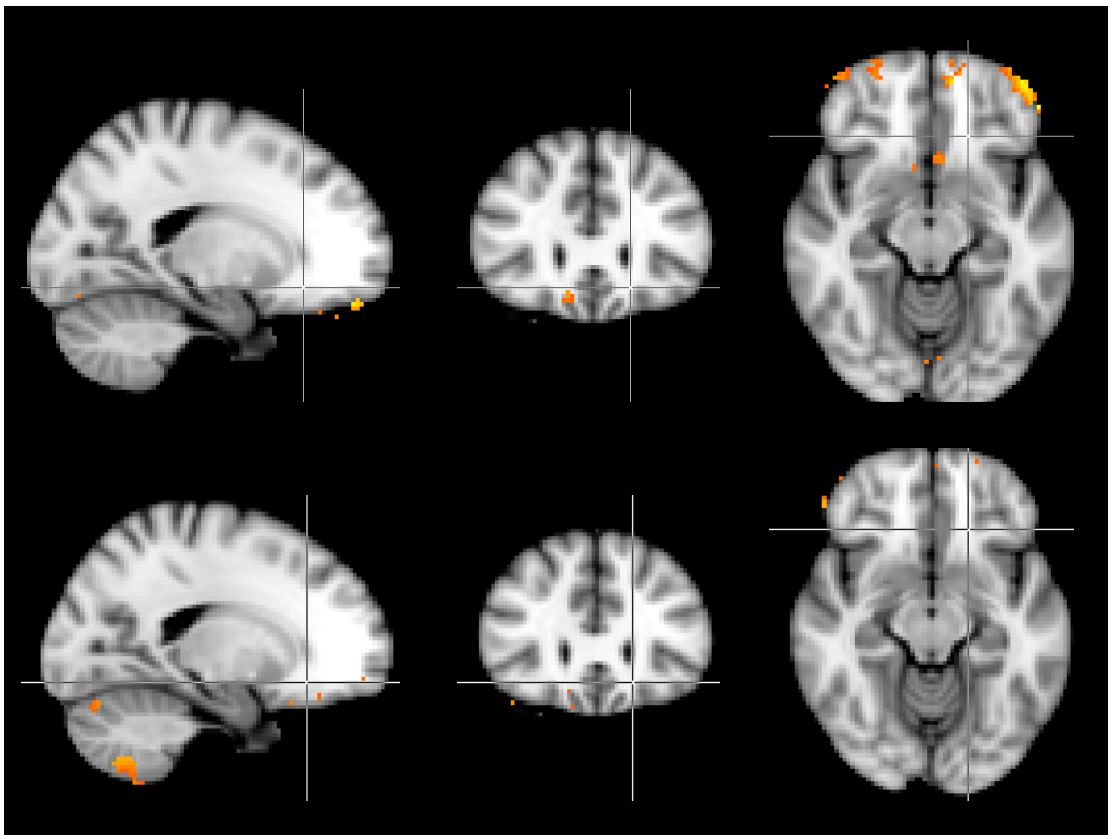


Figure 4. Minimal activation of the frontal pole observed in physical stimulation condition: clitoris (top) and nipple (bottom). Flame 1; cluster $z = 1.0$, $p < 0.01$.

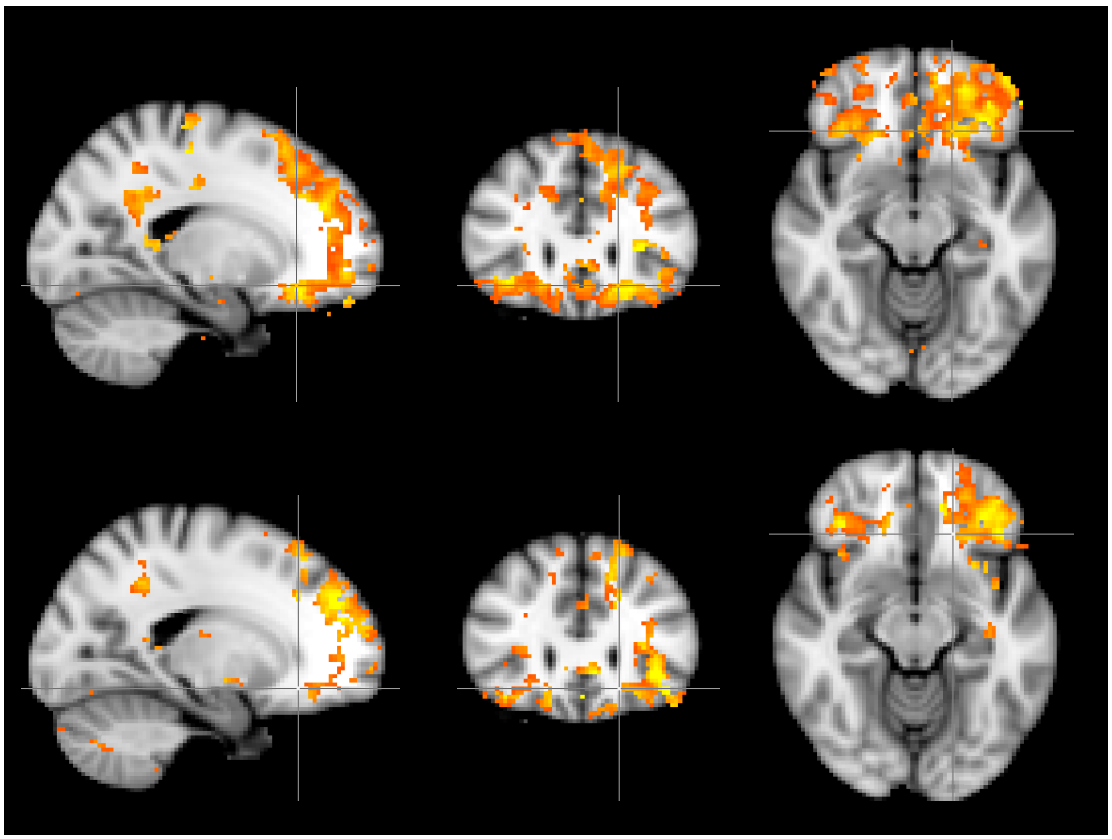


Figure 5. Widespread frontal activation in imagined stimulation condition: clitoris (top) and nipple (bottom). Flame 1; cluster z = 1.0, p < 0.01.

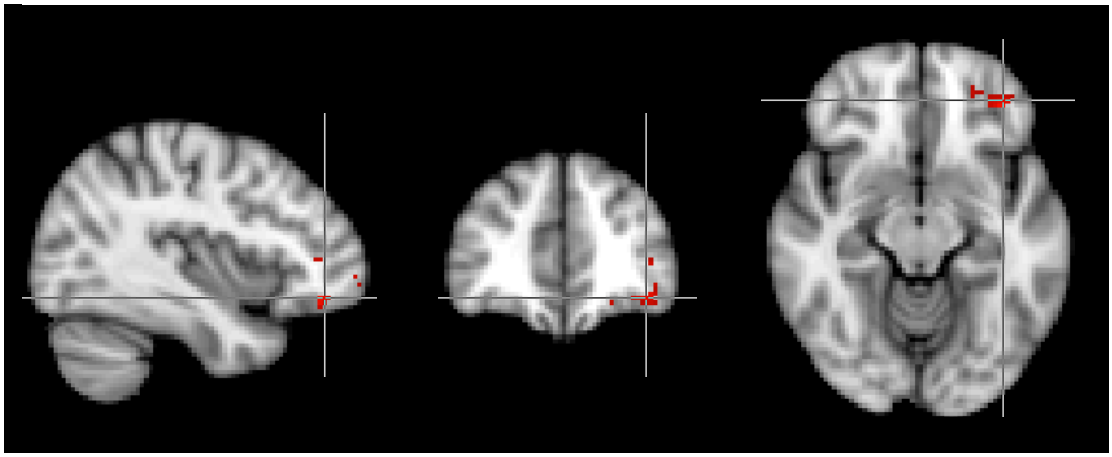


Figure 6. Greater activity in the left frontal pole and orbital frontal cortex for the imagined stimulation condition (clitoris and nipple) than the physical stimulation. Flame 1; cluster z = 1.0, p < 0.01.

C) Primary somatosensory cortex

An area corresponding to the sensory representation of the hand was activated in the left primary somatosensory cortex for all physical simulation conditions. No activity in this region was noted for the imagery contrasts [please refer to Appendix D for additional imagery results].

D) Primary motor cortex

The primary motor cortex was activated in the physical, but not imagined, stimulation condition [please refer to Appendix D for additional imagery results].

E) Secondary somatosensory cortex activation

Activation of the secondary somatosensory cortex (parietal operculum OP1 right) was observed in the clitoris physical stimulation condition (Figure 7), with no activity observed for physical nipple stimulation condition. Activation of the parietal operculum (OP4 left) was observed for imagined stimulation of clitoris and nipple (Figure 8). Comparison of the physical and imagined stimulation condition yielded an area of greater activation in the parietal operculum (OP1 right) for clitoris physical stimulation (Figure 9).

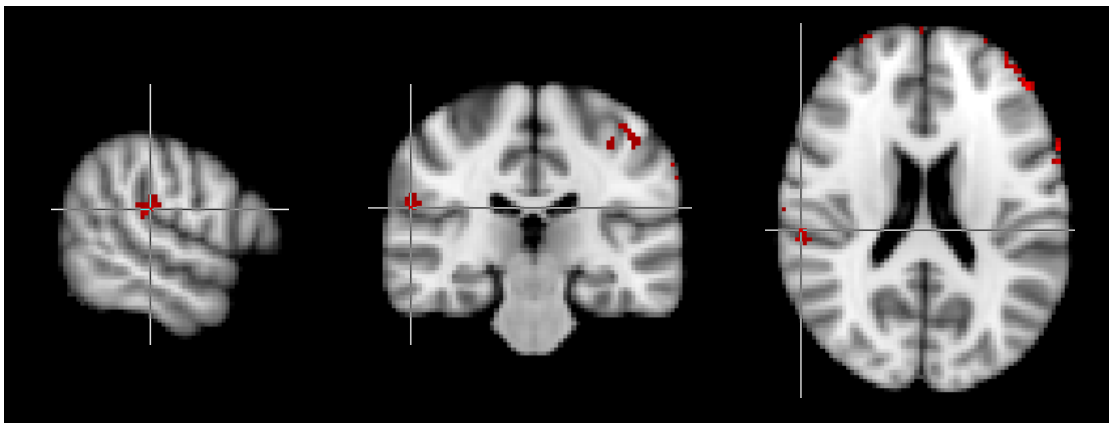


Figure 7. Secondary somatosensory cortex (OP4 right) activated by physical stimulation of the clitoris. Flame 1; cluster z = 1.0, p < 0.01.

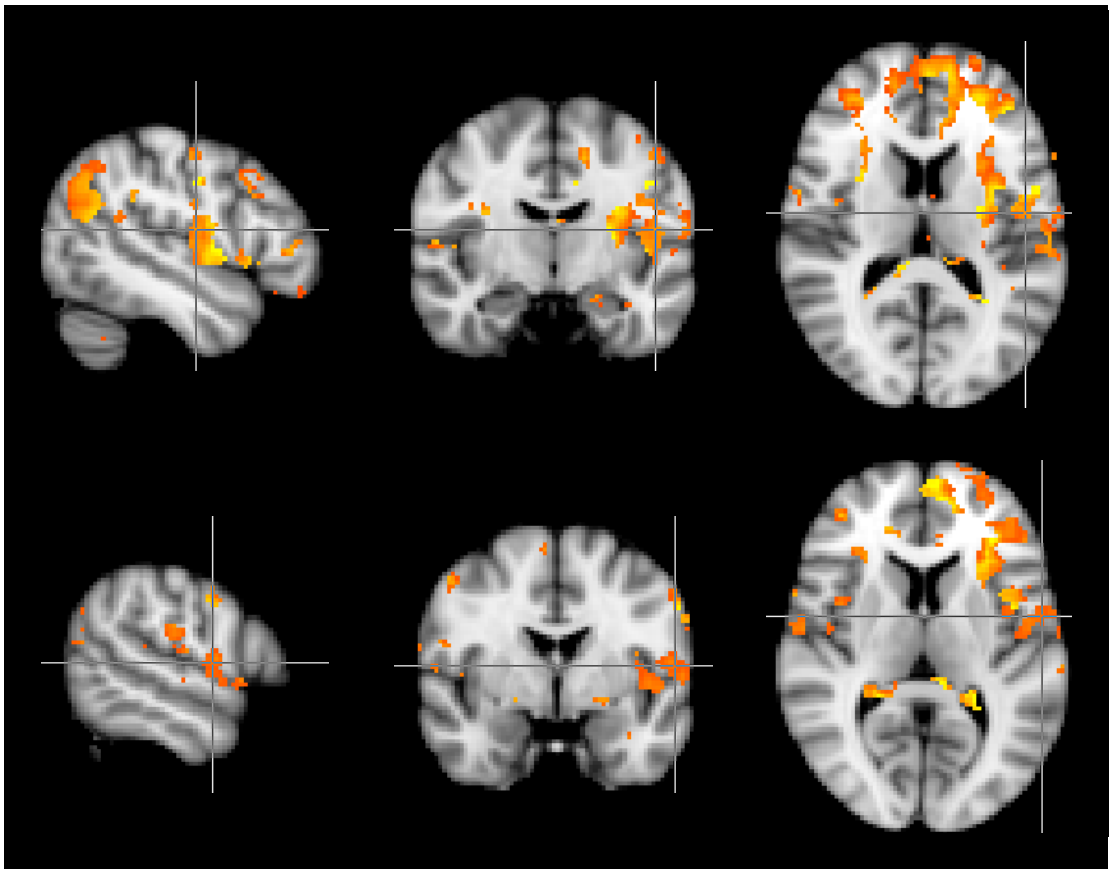


Figure 8. Secondary somatosensory cortex (OP4 left) activated by imagined stimulation of the clitoris (top) and nipple (bottom). Flame 1; cluster z = 1.0, p < 0.01.

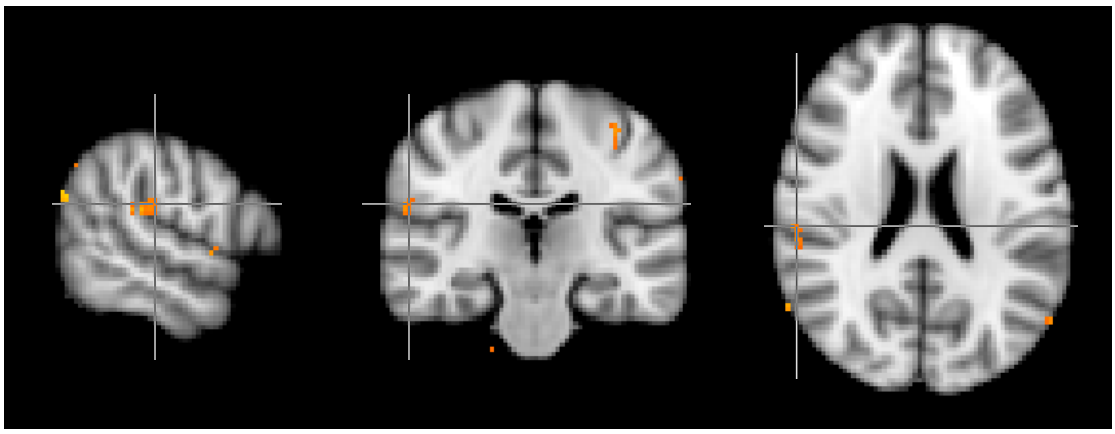


Figure 9. Parietal operculum activation (OP1 right) was greater for physical stimulation of the clitoris than imagined condition. Flame 1; cluster z = 1.0, p < 0.01.

F) Cerebellum

A similar pattern of predominantly right-sided cerebellar activation was observed in both the clitoris and nipple physical stimulation conditions (Figure 10). In comparing clitoris and nipple physical conditions, more left side activation was noted in the nipple stimulation condition [please refer to Appendix D for additional imagery results].

Cerebellar activation was also noted for the imagined stimulation condition, with more activity on the right side for imagined clitoris stimulation, and bilateral cerebellar activity noted for the imagined nipple stimulation (Figure 11).

Comparison of the physical and imagined stimulation contrasts for the clitoris and nipple conditions (Figure 12) indicate significantly more activity in the right cerebellum for the physical stimulation conditions.

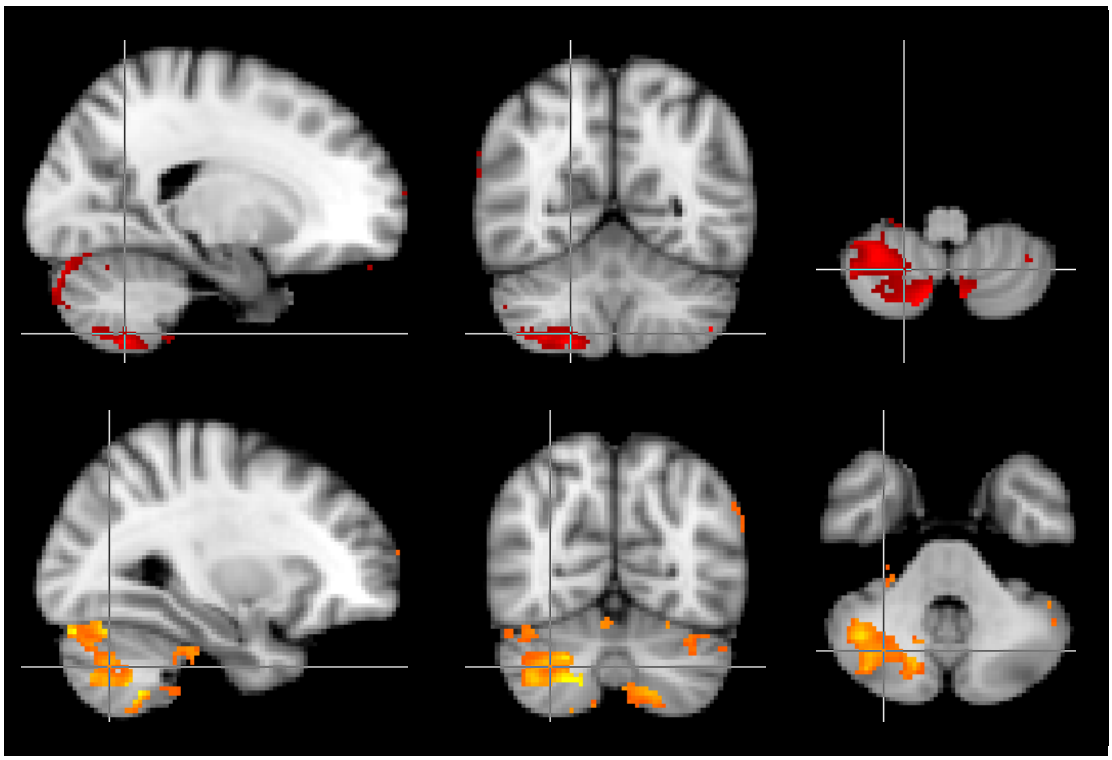


Figure 10. Right cerebellum activation observed in physical stimulation of the clitoris (top) and nipple (bottom). Flame 1; cluster $z = 1.0$, $p < 0.01$.

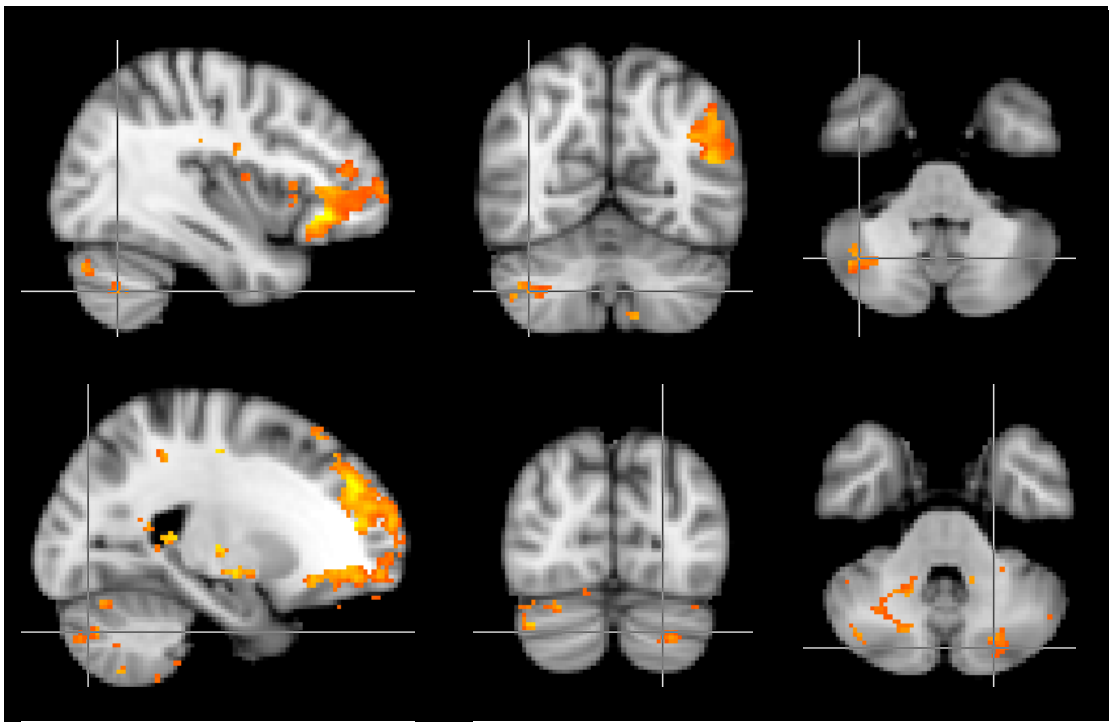


Figure 11. Activity observed in the cerebellum during imagined stimulation of the clitoris (top: right side activation) and nipple (bottom: bilateral activation). Flame 1; cluster $z = 1.0$, $p < 0.01$.

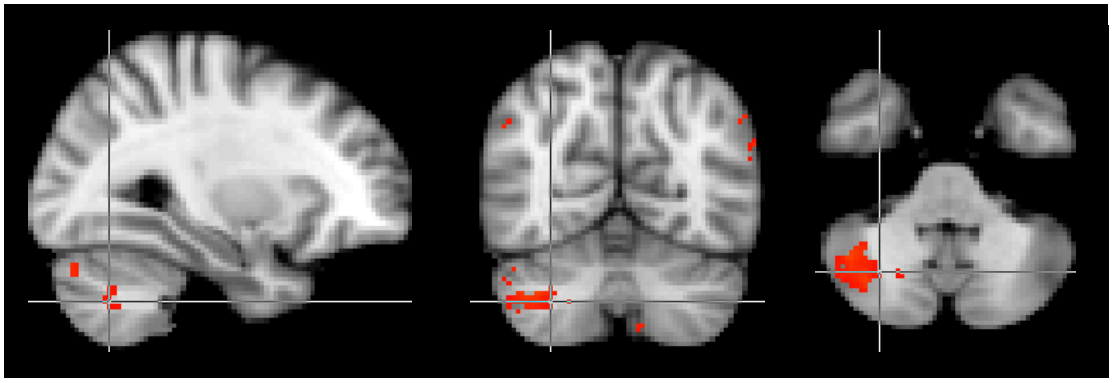


Figure 12. Greater activity in the right cerebellum for the physical stimulation conditions (clitoris and nipple) compared with imagined stimulation. Flame 1; cluster $z = 1.0$, $p < 0.01$.

1.2.2. Activations observed exclusively in imagined stimulation conditions

A) Insular cortex

Activation of the left insula was observed in clitoris imagined stimulation condition, with bilateral activation noted in the nipple imagined stimulation condition (Figure 13).

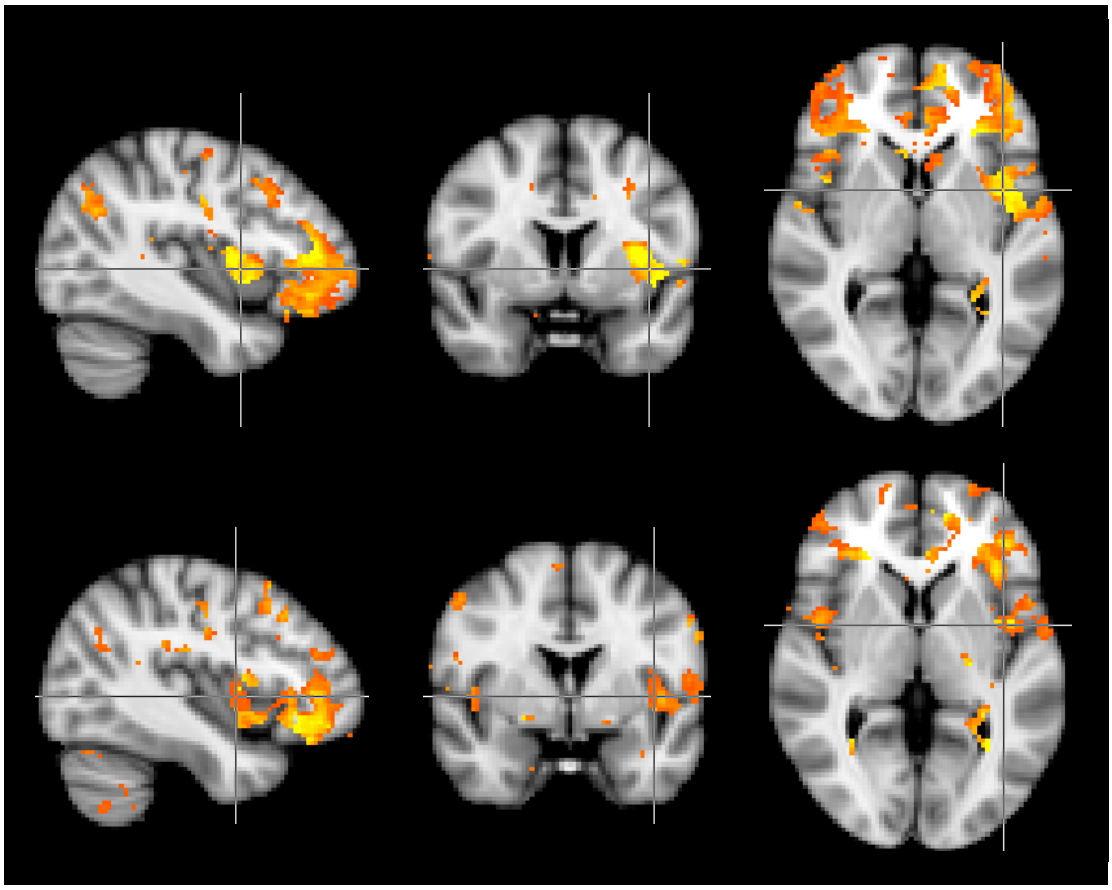


Figure 13. Insular cortex activity observed in imagined stimulation condition: clitoris (top: left side activation) and nipple (bottom: bilateral activation). Flame 1; cluster $z = 1.0$, $p < 0.01$.

B) Amygdala and hippocampus

Activation of the left amygdala was observed for imagined stimulation of clitoris and nipple. In addition, activation of the left hippocampus was noted in the nipple imagery condition (Figure 14).

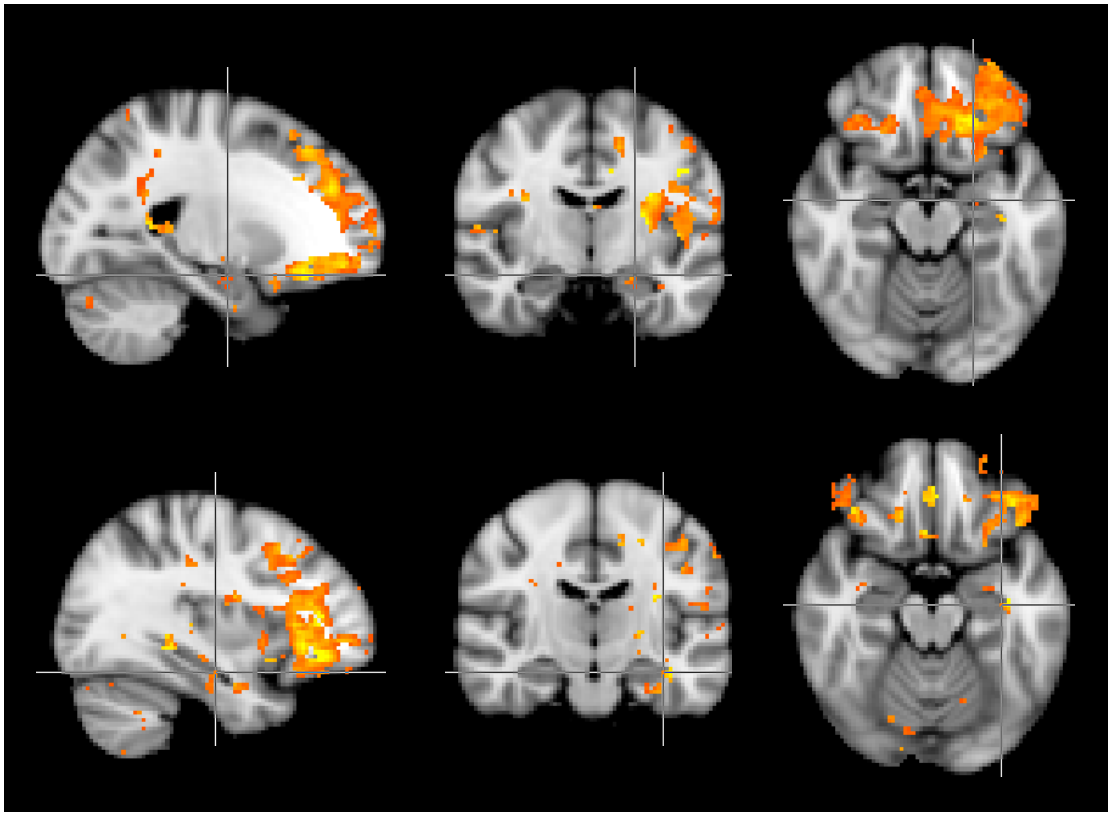


Figure 14. Left amygdala activity observed in imagined stimulation conditions: top (clitoris) and bottom (nipple, with activity also noted in hippocampus). Flame 1; cluster $z = 1.0$, $p < 0.01$.

C) Inferior parietal lobule

A region of activation of the left inferior parietal lobule was observed in the clitoris imagined stimulation condition (Figure 15). A small amount of activation of this region was observed when imagined clitoris stimulation was compared with physical stimulation [please refer to Appendix D for additional imagery results].

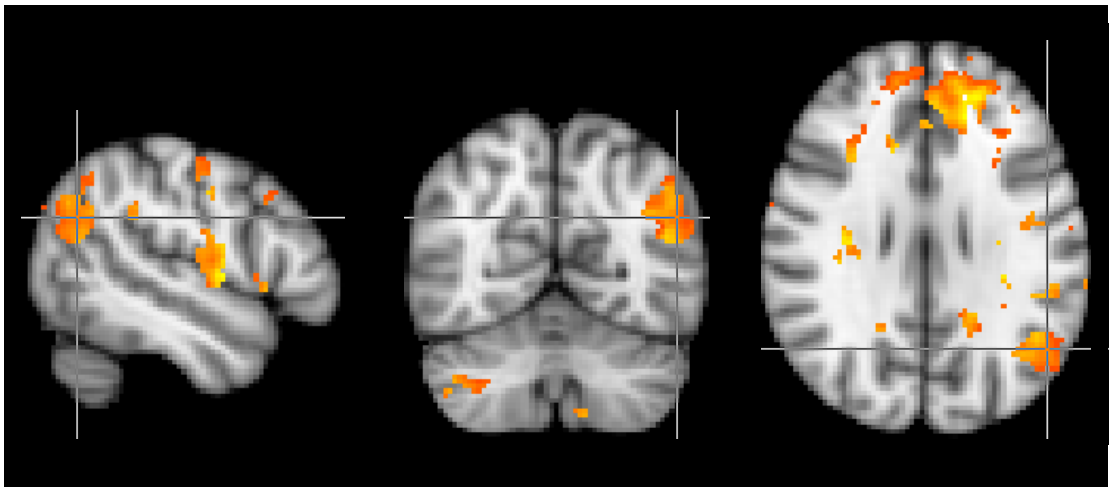


Figure 15. Left inferior parietal lobule activity during imagined clitoris stimulation. Flame 1; cluster $z = 1.0$, $p < 0.01$.

1.2.3. Imagined speculum stimulation compared with imagined dildo stimulation

The comparison imagined dildo stimulation > imagined speculum stimulation revealed significant activation in mesial paracentral lobule and secondary somatosensory cortex (OP4) (Figure 16), thalamus (Figure 17), cerebellum and medulla (Figure 18), frontal (Figure 19) and insular (Figure 20) cortices, amygdala (Figure 21), nucleus accumbens (Figure 22), and hippocampus (Figure 23).

There were no significant differences for the imagined speculum > imagined dildo comparison.

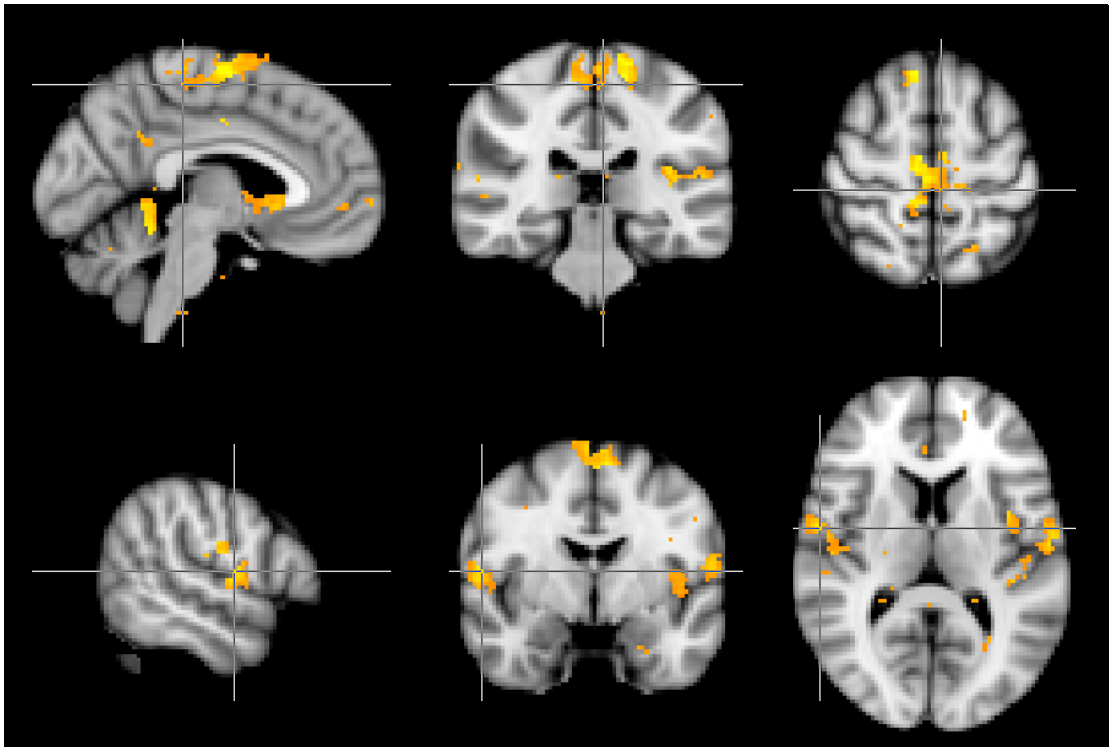


Figure 16. Bilateral activations in paracentral lobule (top) and parietal operculum (OP4) for imagined dildo stimulation greater than speculum imagery. Flame 1; cluster z =1.65, $p < .05$.

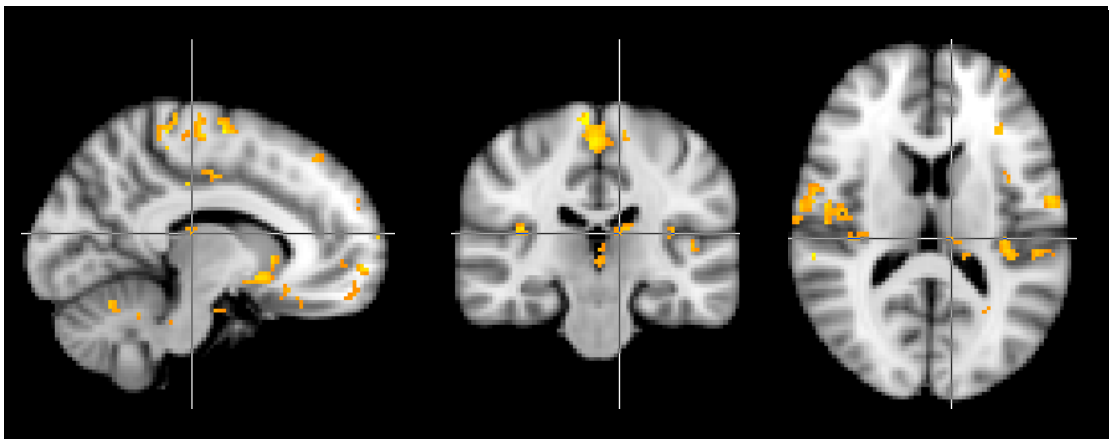


Figure 17. Left thalamus activity greater in imagined dildo stimulation. Flame 1; cluster z =1.65, p < .05.

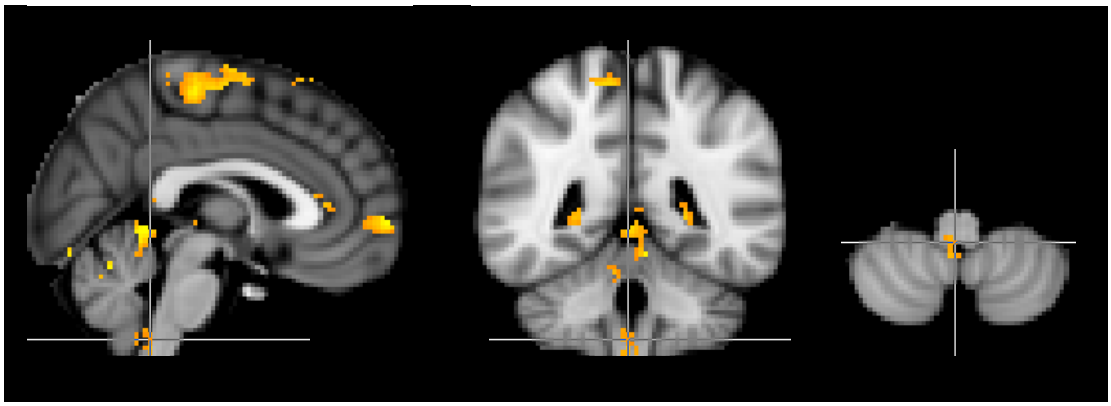


Figure 18. Cerebellum and brainstem activations greater in imagined dildo than speculum. Flame 1; cluster z =1.65, p < .05.

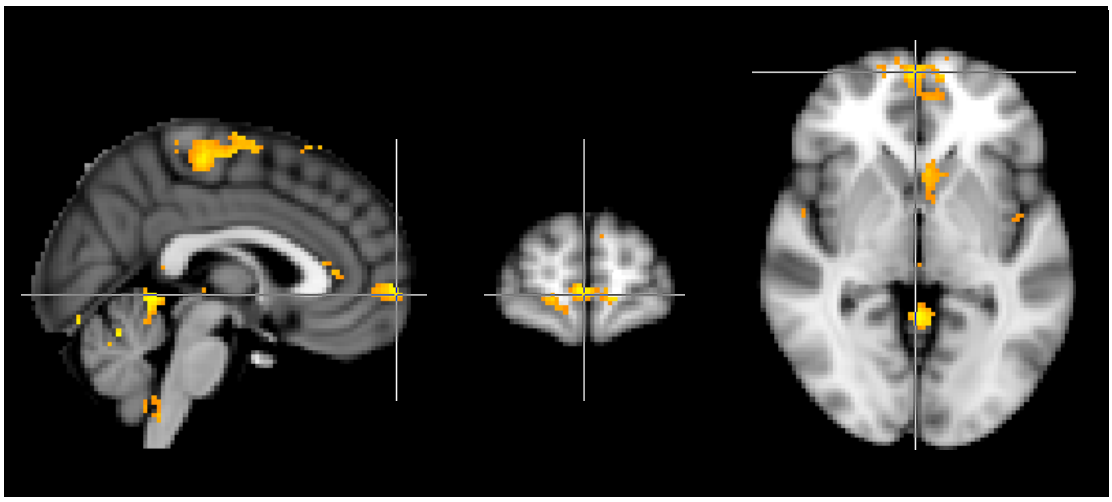


Figure 19. Medial prefrontal cortex activation greater in imagined dildo stimulation. Flame 1; cluster z = 1.65, p < .05.

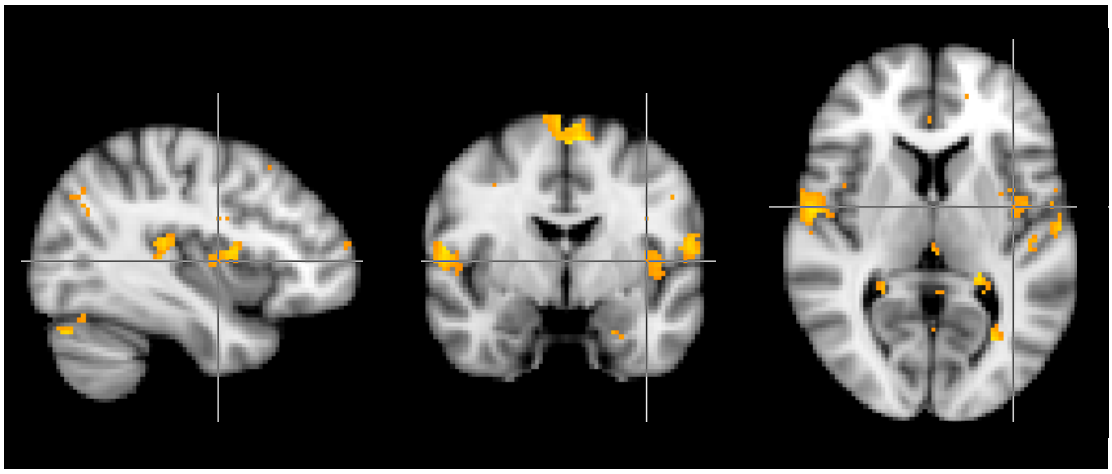


Figure 20. Left insula activation greater for imagined dildo stimulation than speculum imagery. Flame 1; cluster z = 1.65, p < .05.

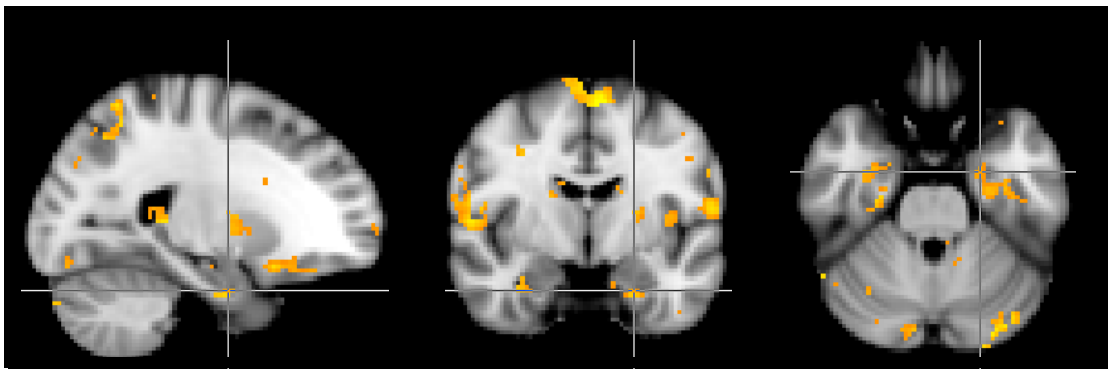


Figure 21. Bilateral amygdala activity greater in imagined dildo stimulation (compared with speculum imagery). Flame 1; cluster z =1.65, p < .05.

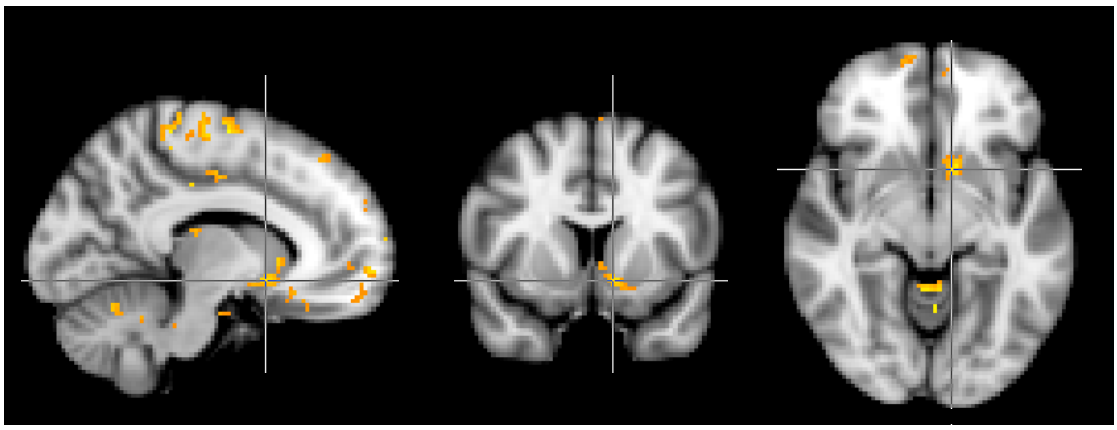


Figure 22. Left nucleus accumbens activity greater in imagined dildo stimulation compared to speculum imagery. Flame 1; cluster z = 1.65, p < .05.

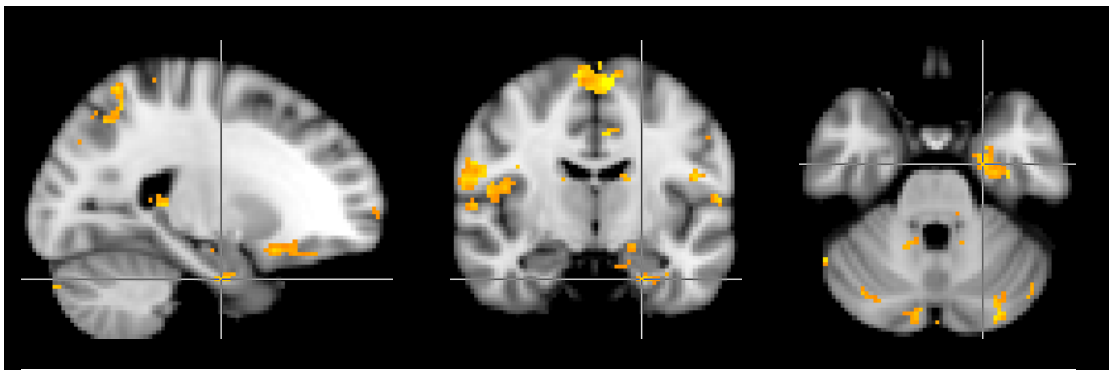


Figure 23. Left hippocampus activity greater in imagined dildo imagery than speculum imagery. Flame 1; cluster z = 1.65, p < .05.

1.2.4. Behavioral Results

1.2.4.1. Imagery and sexual arousal ratings

Table 1. Participants' ratings of vividness of imagery and sexual arousal

	Participant's Ratings (1-low to 7-high)					
	Vividness			Sexual Arousal		
Physical Stimulation	Minimum	Maximum	Mean	Minimum	Maximum	Mean
Clitoris	x	x	x	3.0	7.0	4.8
Nipple	x	x	x	3.0	7.0	5.5
Imagined Stimulation	Minimum	Maximum	Mean	Minimum	Maximum	Mean
Clitoris	3.0	6.0	4.8	1.0	7.0	3.9
Nipple	4.5	7.0	5.3	1.0	7.0	4.1
Speculum	3.0	7.0	5.3	1.0	4.5	1.7
Dildo	1.0	7.0	4.8	1.0	6.0	4.3

As seen in Table 1 the only pairwise comparison that was significant was dildo arousal greater than speculum: $t(8) = 2.56$, $p = .03$. No other pairwise comparisons were significant, i.e., vividness of speculum versus dildo imagery, arousal during clitoris physical versus imagined stimulation, arousal during nipple physical versus imagined stimulation, or vividness of nipple imagery versus clitoris imagery

1.3. Discussion

The present findings support our two main hypotheses: (1) brain regional activity elicited by imagined stimulation of specific body parts overlaps with that elicited by actual physical stimulation; and (2) there are important differences, as well as similarities, in how the brain represents physical and imagined stimulation.

As hypothesized, both imagined and physical stimulation of the nipple and clitoris resulted in activation of the paracentral lobule—the genital sensory cortex, the cerebellum, frontal cortex, and the secondary somatosensory cortex, although in different regions (parietal operculum [OP4] left for imagined stimulation of the nipple and clitoris; OP1 right for physical stimulation of the clitoris).

Support for our hypothesis that there are important differences in the way that the brain represents physical and imagined stimulation was found in the results of the direct comparison of imagined > physical stimulation of the nipple

and clitoris. It is important to note that greater activation of the left orbital frontal cortex and frontal pole were observed for the imagery than for the physical stimulation conditions.

As predicted, physical stimulation of the nipple and clitoris (compared with imagined stimulation) was associated with greater activation of the primary sensory cortex (hand region, left side), primary motor cortex, and cerebellum (right side).

A note on the observed laterality of the cerebellar activation: as participants were using their right hand for self-stimulation, it is probable that the cerebellum was activated predominantly on the right side, as movements of the body have been shown to increase regional cerebral blood flow mainly in the ipsilateral cerebellum. We found that the imagined movements also resulted in ipsilateral activation of the cerebellum, but to a lesser degree, consistent with previous findings (Jueptner et al, 1997).

Although it was expected that the insula and the primary and secondary sensory cortices would be activated in the imagined stimulation conditions, it was predicted that these activations would be significantly less than observed in the physical stimulation conditions. Imagined stimulation of the nipple and clitoris (but, unexpectedly, not the physical stimulation conditions) resulted in activation of the left insular cortex (in the case of the nipple, bilaterally), the left amygdala, and, for nipple, the left hippocampus. Thus, the imagined stimulation of the clitoris and nipple activated a subset of the regions involved in sensory processing, sexual sensation, and orgasm, while the actual physical stimulation

did not. These results are inconsistent with our predictions and with the results of other studies (Yoo et al., 2003: Olivetti Belardinelli et al., 2009: Wise et al., 2010).

We predicted that the physical stimulation conditions would result in greater activation of the paracentral lobule (genital sensory cortex) than the imagery conditions. Contrary to our expectations, there were no significant differences observed between the imagined and physical stimulation conditions.

Remarkably, and unexpectedly, imagining dildo stimulation generated extensive brain activation, whereas imagining speculum stimulation generated virtually no brain activation. This may be a function of the difference in mental attitude toward the two different stimuli.

There were no significant regional differences for the contrast imagine speculum > dildo.The dildo imagery, however, was rated as signifcantly more sexually arousing than speculum imagery, ($t(8) = 2.56$, $p = 0.03$, but not significantly more vivid, which suggests that the degree of sexual arousal may be more salient than the vividness of imagery in terms of how the brain represents the imagined stimulation. Furthermore, no participants rated any of the imagery conditions as aversive, thus it is not likely that the difference between the dildo and speculum imagined stimulation conditions are a result of the speculum imagery being aversive.

Thus, as hypothesized, just imagining stimulation by a dildo activated multiple brain regions implicated in the processing of bodily sensation, sexual stimulation, reward, and orgasm (Komisaruk et al., 2004, 2005). As will be shown in the findings of Experiment 2: “Brain regional activation upon transition

to self- and partner-induced orgasm in women: an fMRI analysis of orgasm in women", many of the same brain regions activated in the imagined dildo > speculum contrast were also activated during the course of genital stimulation that culminated in orgasm.

As predicted, the paracentral lobule -- the genital sensory cortex -- was activated (bilaterally), as was the secondary somatosensory cortex -- the parietal operculum -- in OP4. The OP4 region has previously been shown to have somatotopically organized body maps for hands (Eickhoff et al, 2006 a), feet (Young et al., 2004), penis (Kell et al, 2005), and anus (Eickhoff et al., 2006a).

In addition to these primary and secondary somatosensory cortical activations, the left thalamus, left insula, left hippocampus, left nucleus accumbens, bilateral amygdala, cerebellum, medulla, and the medial frontal cortex were activated in the imagine dildo condition compared to the imagine speculum condition.

There appear to be discrepancies in the results of the comparison between imagined and physical stimulation of the clitoris and nipple, with greater than expected activity observed in the imagery contrasts, and less robust activations than expected in physical stimulation contrasts, even though the participants subjectively rated the physical stimulation of the nipple and clitoris (5.5 and 4.8) as sexually more arousing than the corresponding imagined stimulation (4.1 and 3.9). These discrepancies were reduced, but not eliminated, once the results were contrast-masked to ensure that the resulting comparisons reflected only positively driven changes in the BOLD signal.

These discrepancies may arise, in part, from procedural differences in this current study compared to previous studies (Wise et al., 2010; Komisaruk, Wise, et. al, 2011; Yoo et al., 2003; and Olivetti Belardinelli et al., 2009) that employed a boxcar, blocked design with stimulation periods (physical and imagined stimulation) contrasted with "rest," each block of trials conducted in separate functional runs. We hypothesized that the use of explicit rather than implicit modeling would make the experimental and control conditions as similar as possible, thereby allowing a finer-tuned discrimination between the physical conditions (nipple and clitoris stimulation) and how these regions were represented in terms of imagined stimulation.

It is possible that the "explicit" modeling control conditions were very effective – indeed, so similar to the experimental conditions as to minimize the differences between them, particularly in the case of the physical stimulation trials. In other words, when the participants were "modeling" stimulation by moving their fingers together over their nipple or clitoris (without touching the target body part), the actions of doing so might have conjured a potent mental image of that body part, thereby obscuring any difference between modeling and stimulating. Thus, the physical actions of modeling involved in the physical stimulation trials may have been more evocative of sensations of the nipple or clitoris than simply "thinking" about making these movements, as in the case of the imagery trials.

Another possible explanation of the lower than expected activity observed in the physical stimulation contrasts is that this may have arisen from a

combination of habituation -- a drawback of block designs -- and fatigue. As the physical stimulation conditions followed the imagery tasks, the participants may have become fatigued from repetitively imagining “modeling” movements or imagining “stimulation,” without rest. By the onset of the physical stimulation trials, their brain response to the stimulation may have been attenuated, although they still subjectively rated the physical stimulation trials as sexually arousing. This may have contributed to a higher global mean baseline making it necessary to contrast-mask the results of the differential contrasts with only positive voxels.

Despite this rationalization for the relatively weak genital sensory cortical response to physical genital stimulation, this emphasizes further the remarkable unexpected strength of the activation of the genital sensory cortex just by imagery.

The imagine speculum > imagine dildo findings may have been more robust than the imagined and physical stimulation of the clitoris and nipple findings for a number of reasons. Prior to the presentation of these conditions, the participants had a brief rest, permitting them to recover from any fatigue occurring during the previous blocks. This task introduced some novelty to the experimental paradigm, as the participants were instructed to think about someone else delivering the stimulation. Moreover, since these conditions involved only a short period of alternating speculum imagery with dildo imagery, there was no time for habituation. In addition, as there was no “model” condition as a control, the contrast between the imagine speculum (vivid, but not arousing) and dildo (not as vivid, but more arousing) consequently may have been clearer.

Another factor that could have contributed to the lack of robustness of the physical stimulation results may stem from characteristics of the study's participants. This experiment occurred during the context of an orgasm study. All participants described themselves as being "consistently highly orgasmic" during study enrollment. As there has been support in the literature for a correlation between orgasm reliability and higher hypnotic suggestibility (Bridges, et al., 1985), and imagery ability (Harris et al., 1980), the degree of suggestibility of these participants may potentially have biased the results toward more robust imagery activations than expected. This may have contributed to the lack of robustness of the brain response to the physical stimulation conditions by having the explicit modeling be too suggestive of the actual physical stimulation.

The major limitation of this study, therefore, arises from the lack of robustness of the results for the physical stimulation of the nipple and clitoris. The cluster-forming threshold needed to be reduced in order to discern differences between the stimulation and modeling conditions, potentially weakening the conclusions we can draw from this part of the study. This may have also compromised our ability to clearly differentiate between the physical and imagery "maps" for the clitoris and nipple within the primary and secondary somatosensory cortices.

The results, especially in the case of the imagine dildo > imagine speculum contrast, provide strong support for the capacity of imagery to activate brain regions implicated in the processing of bodily sensation, sexual stimulation, reward, and orgasm. This may be the mechanism underlying the ability of some

women to induce orgasm by imagery alone, in the absence of physical stimulation (Whipple et al., 1991). Overall, the results are consistent with those of our previous study (Komisaruk, Wise, et al, 2011), localizing the sensory representation of the physical stimulation of nipple and clitoris to the genital sensory cortex (the mesial paracentral lobule), and now extending this finding to include the representation of imagined stimulation of these body parts.

Resolving further questions regarding the somatosensory maps for physical stimulation of the female body could help clarify the underlying neurological basis of sex differences, and will be crucial in the development of effective treatments for disorders that predominantly or exclusively affect women, such as Persistent Genital Arousal Disorder (Leiblum & Nathan, 2001), pelvic pain conditions, and vulvodynia (Di Noto et al., 2012).

In the future, an understanding of the somatosensory maps of mental imagery could conceivably lead to new treatments for these and other disorders afflicting both men and women. This knowledge could also pave the way to clarifying the role that the sensory cortical representation of the female genitals may play in anorgasmia, hypoactive sexual desire disorder, and other sexual disorders suffered by women.

Many questions remain unanswered as even more questions are generated. For example, why do we see bilateral activation of the paracentral lobule in some imagery conditions but not in the physical stimulation conditions? In addition to the frontal, parietal, and somatosensory cortices, what roles do other brain regions play in imagery? Can there be instances in which imagined

stimulation of the nipple and clitoris is truly more potent in terms of the magnitude of elicited brain activity than physical stimulation? Is the ability to powerfully stimulate brain regions involved in bodily sensation, sexual stimulation, reward, and orgasm by imagery alone limited to people with high levels of hypnotic suggestibility or vividness of imagery, or can the general population learn this?

What is the significance of the preponderance of the left-sided activity in the amygdala, insula, hippocampus, and frontal regions noted in the “sexually arousing” imagery conditions? Could this be related to recent findings that increased activity in left temporal and frontal brain regions is associated with an enhanced responsivity to rewarding and positive stimuli (Davidson, 1992; Tomarken & Keener, 1998)? There is increasing evidence that frontal asymmetry is involved in emotional regulation (Allen et al, 2001). Real-time functional magnetic resonance imaging (rtfMRI), in conjunction with EEG, has been therapeutically applied as a tool for neurobiofeedback, with the goal to increase activity in the left amygdala (Zotev et al., 2014) and insula (Veit et al., 2012), regions that are associated with enhanced mood regulation and reduced symptoms of anxiety and depression. Could pleasurable tactile imagery be a low-tech way of enhancing mood states? Will the work being done with rtfMRI lead to insights about potential therapeutic applications of imagery?

ABSTRACT

Brain regional activation upon transition to self- and partner-induced orgasm in women: an fMRI analysis

This study addressed a major discrepancy in the literature regarding whether frontal and temporal cortical regions are activated (Komisaruk et al., 2004; 2005) or deactivated (Georgiadis et al., 2006; 2009) during orgasm. In addition to the different methods used (fMRI versus PET, respectively), a major procedural difference was that genital *self*-stimulation was employed in the fMRI studies, while genital *partner-applied* stimulation was used in the PET studies. We suspected that the discrepancy was due not to fMRI versus PET technology, but rather to the *activation* of the frontal and temporal cortices in executing the *self*-stimulation in contrast to their *deactivation* due to what Georgiadis et al considered to be "surrender" to stimulation by the *partner*. We hypothesized, assuming that both groups' findings were valid, that the frontal and temporal cortices would become *activated* during a woman's *self*-stimulation induced orgasm, whereas they would become *de-activated* during the woman's *partner*-induced orgasm. Ten healthy women (age range 29 -74), and their male partners participated in the current study. Contrary to our hypothesis, we found no deactivation of frontal or temporal regions during partner stimulation-induced orgasm (or, for that matter, during self-stimulation-induced orgasm). Nor did we

find evidence that activity of the frontal and temporal regions decreased at orgasm in relation to the time period immediately before. As no significant regional brain differences were observed during orgasm between the two stimulation conditions, the data for both groups were combined. This revealed widespread activation throughout the brain, with different regional patterns related to the sequence leading up to, during, and after orgasm; these included activation of primary sensory, motor, sensory-motor integration, and reward regions.

2. Introduction

There is a paucity of neurobiological research on human sexual activity, even though this knowledge could potentially have widespread applications in the treatment of sexual disorders, and contribute to further elucidating the complex systems involved in pain, pleasure, and reward. In particular, studies of the human orgasm are sparse, most likely due to the considerable methodological difficulties this work presents, along with cultural constraints. As a result, presently there are only two laboratories that conduct systematic studies of the regional brain activity leading up to and including orgasm in the female human--the Komisaruk group at Rutgers University, using functional magnetic resonance imaging, (Komisaruk, Whipple et al, 2004; Komisaruk & Whipple, 2005; Komisaruk, Wise et al, 2010, 2011; Wise et al., 2012) --and the Holstege and Georgiadis group, in the Netherlands, using positron emission tomography, (Georgiadis et al., 2006; 2009; Huynh et al., 2013).

The goal of the present study is to resolve a discrepancy in the literature arising from conflicting results coming from these two laboratories.

Our laboratory, the Komisaruk group, has consistently found widespread, regional brain activation leading up to and peaking at orgasm, including frontal and temporal brain regions, while conversely, the Georgiadis group report diametrically opposite results in which the frontal cortex—specifically the right medial orbitofrontal, left lateral orbifrontal, and left dorsolateral cortices—and right amygdala were *de*activated during orgasm. And also in contrast with our findings of widespread activation during orgasm, the Dutch group has reported

finding reliable orgasm-related activation only in the cerebellum (Georgiadis et al., 2006), and more recently, the pons (Huynh et al., 2013)

In addition to the different methods employed (fMRI versus PET), a major procedural difference was that genital *self*-stimulation was employed in the Komisaruk studies; while genital *partner-applied* stimulation was used by the Dutch group. In order to test the possible significance of this procedural difference and hopefully resolve the discrepancy over brain activation or deactivation at orgasm, in the present study we compared the activity of frontal cortex, amygdala, and other brain regions during genital *self*-stimulation-induced orgasm with *partner*-stimulation-induced orgasm in order to control for this potentially crucial procedural difference.

A second goal of this study was to address two valid methodological critiques of our previous orgasm studies: that our results potentially (1) reflect artifact created by excessive head movement, and (2) are compromised by the lack of correction for multiple statistical comparisons.

The current study incorporates new methods to increase the validity of our findings. We have developed a custom-made head-stabilization system in order to significantly decrease the amount of head movement at acquisition, and then, for data analysis, we use a recently developed statistical tool to detect and remove time points that may be corrupted by motion. Finally, our results are corrected for multiple comparisons by using appropriate cluster-forming thresholds.

Another challenge encountered in the study of orgasm lies in the inherent variability of the duration of stimulation, orgasm, and recovery. This is a factor that may have contributed to our prior difficulty reaching significant, corrected results at the group level. The current study addresses this variability by sampling equivalent time points across participants that reflect comparable phases of early stimulation, mid-stimulation, late stimulation, orgasm onset, and recovery. Thus, this approach permits the sampling of comparable phases during the orgasm sequence that reflect processes that have different time courses for different individuals.

Regarding whether the frontal regions would be activated (Komisaruk et al., 2004, 2010, 2011) or deactivated (Georgiadis et al., 2006, 2009) during orgasm, we hypothesized that the results of self-induced orgasm would differ from partner-induced orgasm. As participants must plan and execute the motions for masturbation during the self- induced orgasm sequence, there might be increased activity in “executive” brain regions such as the dorsolateral prefrontal cortex when compared to the partner-induced orgasm, during which the participants are not planning and executing their own stimulation.

Based on the results of our previous time course study (Komisaruk, Wise et al. 2010), we expected that the current study would show that different brain regions are active, and to different degrees, over the course of stimulation, orgasm and recovery as a result of the different underlying neural processes involved. We predicted that the activity of some brain regions would appear to increase gradually with early activation (amygdala, hippocampus,

and caudate head), others would show an increase of activity later, building over the course of self-stimulation (paracentral lobule- genital sensory cortex, thalamus, and substantia nigra), and some areas would show phasic activation just before orgasm (cerebral tonsil, anterior cingulate cortex, and inferior frontal gyrus), or at orgasm (nucleus accumbens and hypothalamus).

Based on our earlier findings, we expected that orgasm induced by both self and by partner would result in similar significant activity in the caudate, hippocampus, amygdala, substantia nigra, cerebellar tonsil, and anterior cingulate cortex, which would increase in the later phases of stimulation, and that activity in the nucleus accumbens and hypothalamus would peak at orgasm for both types of orgasm.

What happens in the brain that initiates and orchestrates the “going over” from stimulation to orgasm? This is of interest for clinical applications for individuals suffering from the inability to experience an orgasm. We attempted to elucidate this by comparing the stimulation period that immediately precedes the onset of orgasm with that at the onset of orgasm.

In the present study we also sought to identify the sequence of brain regions activated (or deactivated) in the processes of genital stimulation, orgasm, and recovery, so that these reliable regions of interest could be used to in future effective connectivity analysis to ascertain how the various brain regions interact to create the complex phenomenological experiences culminating in orgasm.

2.1. Methods

2.1.1. Research participants

Fourteen healthy women were recruited for this study by world of mouth. Data from two of the participants had to be excluded because they were unable to experience orgasm during the scanning session. Two additional data sets had to be discarded: one because of excessive head movement, and the other due to problems with fields of view at acquisition. Data from 10 participants were used, (age range 29-74 years, mean = 43.6, SD =14.9 years). Six of the women reported being in a significant relationship; three stated that they have children. The participants each gave informed consent per the Rutgers University Institutional Review Board for this approved study. Each participant also granted the investigator the optional permission to use her interview statements anonymously for presentations and publications. The scanning session took place at the Rutgers University Brain Imaging Center (RUBIC, Newark, NJ), in compliance with all RUBIC MRI common practices. The participants were prescreened for MRI safety and complete screening forms as per RUBIC requirements, including the pregnancy release form. Prior to the scanning session, each participant reviewed the scheduled protocol for practice such that she was familiar with the different physical and imagery tasks she was asked to perform during the experiment. Participants were compensated $50 for their participation in the study.

Each of the 10 women whose data were used for the study brought a male partner to the study to provide the genital stimulation for the partner stimulation-

induced orgasm sequence. Each of the male partners were prescreened to determine suitability for study participation and gave informed consent per the Rutgers University Institutional Review Board for this approved study. In compliance with all RUBIC MRI common practices, the male participants were prescreened for MRI safety and completed screening forms per RUBIC requirements. Prior to the scanner, the male participants reviewed the study protocol to prepare them for their role in the experiment. Male participants were compensated $50 for study participation.

2.1.2. Experimental paradigm

Study 2 took place immediately upon completion of Study 1: “Activation of sensory and other brain regions in response to imagined genital versus physical genital stimulation.” In designing Study 2, the plan was to counterbalance the order of the orgasm conditions such that half of participants would be assigned to complete (a) genital self-stimulation induced orgasm first, followed by (b) orgasm induced by partner stimulation. The other half of participants would attempt the orgasm induced by partner stimulation first, prior to the orgasm induced by genital self-stimulation. The plan to counterbalance the order of the orgasm conditions was made in order to avoid potential order effects.

To avoid confusion and permit participants and their partners to prepare for the experiment, they were informed in advance of the scanning procedure as to which orgasm condition they would be asked to attempt first. Although every

effort was made to counterbalance the order of the orgasm conditions, some participants expressed a strong preference for which condition of orgasm to have first. These requests were accommodated as indicated.

2.1.2.1. Protocol for self-induced orgasm

Participants assigned to complete the self-stimulation orgasm condition first followed instructions presented to them visually on an fMRI-compatible computer projection screen. First, the participant saw the instruction "*rest*," which lasted 60 seconds. Then the instruction, "*Press when start stimulation*" appeared, which cued her to press the button once she began genital self-stimulation. After the participant pressed the button to indicate she was self-stimulating, the words "*Press when orgasm begins*" appeared on the screen to cue her to press the button when her orgasm started. Once the participant pressed the button to indicate the onset of orgasm, the instruction "*Press when orgasm ends*" appeared to cue her to press the button when her orgasm was finished. Once the participant pressed the button to indicate that her orgasm ended, the instruction "*Press button when recovered"* appeared to cue her to press the button when she felt physically recovered from the orgasm (back to baseline). Once the participant indicated by button press that she had recovered, the instruction "*Relax"* appeared, cueing the participant to lie still for five minutes.

At the end of the five minutes of rest, the participant saw the instruction, "*Imagine Speculum'* " appear on the screen for 30s, which cued her to *think*

about someone inserting a speculum into her vagina, followed by instructions to "*Imagine Dildo,*" cueing her to *think* about being penetrated by a dildo for 60 s. Finally, the instruction "*Imagine Speculum"* cued her to think about the speculum condition for another 30 s, completing the genital self-stimulation-to-orgasm trial.

The protocol for the participants who were assigned to complete the genital self-stimulation-induced orgasm condition following the partner-stimulation orgasm condition was identical, with the exception that they would start the protocol *after* completion of the partner-stimulation-induced orgasm.

2.1.2.2. Protocol for partner-induced orgasm

Participants assigned to complete the partner-stimulation orgasm condition first followed instructions presented to them visually on the projection screen, as described in the procedure for genital self-stimulation-induced orgasm.

The male participants remained in the scanning room throughout all experimental conditions, although they only participated in this segment of the experiment. They were cued via pre-recorded auditory instructions delivered via headphones that were prompted by the responses of the female participants linked electronically (triggered by the start of the scan) with the experimental tasks.

The female participants first saw the instruction to "*rest*," which lasted 60s. The male participant then heard the instruction "prepare to begin

stimulation" during this period. Then the instruction, "*Press when partner starts stimulation*" appeared to cue the female participant to press the button when her partner began to stimulate her genitals. The male participant then heard the instruction, "start stimulation." After the female participant pressed the button to indicate that her partner had begun stimulating her genitals, "*Press when orgasm begins*" appeared on the screen to cue her to press the button when her orgasm began. Once the participant pressed the button to indicate she had begun to orgasm, the male participant heard the feedback, "your partner's orgasm has begun." The female participant then saw, "*Press when orgasm ends*" appear on the screen to cue her to press the button when her orgasm finished. Once the participant pressed the button to indicate that her orgasm had ended, the male partner heard the instruction, "stop stimulating, your partner's orgasm has finished." The female participant then saw the instruction, "*Press button when recovered* " appear to cue her to press the button when she felt physically recovered from the orgasm (back to baseline).

At that point, the male participant heard the instruction "rest to the end of the experiment." Once the female participant had indicated by button press that she was recovered, the instruction "*Relax"* appeared, cueing the participant to lie still for 5 min.

At the end of the 5 min of rest, the participant saw the instruction, "*Imagine Speculum'* " appear on the screen for 30s, which cued her to *think* about someone inserting a speculum into her vagina, followed by instructions to "*Imagine Dildo,*" cueing her to *think* about being penetrated by a dildo for 60

s. Finally, the instruction "*Imagine Speculum"* cued her to think about the speculum condition for another 30s, completing the genital self-stimulation-to -orgasm trial.

The protocol for the participants who were assigned to complete the partner-induced orgasm condition following the self-stimulation orgasm condition was identical, with the exception that they would start the protocol *after* completion of the self-stimulation-induced orgasm.

All female participants were debriefed following the scanning session and interviewed regarding their experience as approved by the IRB [please refer to Appendix C for Interview questions].

2.1.3. FMRI acquisition

The fMRI scans were performed at the Rutgers University Brain Imaging Center using a 3T Siemens Trio with a Siemens 12-channel head coil. For registration purposes, anatomical images were acquired using magnetization prepared rapid gradient echo (MPRAGE) sequences (176 slices in the sagittal plane using 1mm thick isotropic voxels, TR/TE = 1900/2.52ms, field of view = 256, 256 x 256 matrix, flip angle = 9 degrees; 50% distance factor). Gradient-echo EPI sequences were acquired of the whole brain including the entire medulla oblongata (33 slices in the axial plane using 3mm isotropic voxels, TR/TE = 2000ms/30ms, interslice gap = 1.5 mm, flip angle = 90, field of view = 192, 64x64).

2.1.3.1. Head immobilization system

The problem of head movement during genital self- and partner-induced stimulation and orgasm was reduced to an average of 1-2mm through the use of a combination of two different types of commercially-available head immobilization devices: The Ossur Philadelphia Tracheotomy Collar (two-part polyurethane foam with Velcro fasteners; all plastic) plus the Aquaplast Thermoplastic mesh Radiology Mask. (The Aquaplast frames are too wide for the Siemens Allegra head cradle, so for each participant it was first necessary to cut the frames down by approx. 1 cm on all sides, and finish them smoothly; this was accomplished using an electric disc “cutoff” tool and finishing the frames with a bench grinder and buffing wheel with polishing compound). The collar (3 sizes, matched to each participant) was first adjusted under the chin to set a face-forward posture with the participant sitting upright, the Velcro straps were fixed and their positions were marked with a felt pen. While wearing the collar, the participant then lay down supine on an exercise mat on a table, and one (of the two) thermoplastic mesh masks was softened in a hot water bath (approx. 50 degrees C, like a hot towel), positioned under the participant’s head such that the lower portion of the thermoplastic mesh covered the upper part of the collar and then the rigid frame of the mask was brought up around both the back of the head and the collar to the level of the ears, which were tucked into the mask. The mask was then form-fitted to the head and the collar by gently pushing it with the fingers all around the head, the neck and the collar continuously as the thermoplastic cooled and set rigidly into position. The cooling of the

thermoplastic to rigidity takes about 2 minutes. The second thermoplastic frame was then heated in the water bath and fitted to the participant's face and front of the collar. The thermoplastic was gently pushed with the fingers, with the help of the participant, to form-fit to the forehead, side of head, nose, cheeks, mouth, chin, and front and under-chin portion of the collar, and its frame was brought to congruence with the frame of the thermoplastic mask that cradled the back of the head, leaving a gap of about 1cm all around between the two frames. (The gap enabled us to tighten the mask slightly as necessary in the fMRI scanner, as the head always shifts slightly upon removing and then re-fitting the entire assembly). For the participant's comfort, the portion of the face mask covering the eyes, nostrils, and mouth were first marked with a felt pen, then the front (face) half of the mask was removed from the participant and an electric "Dremel" tool with side-cutting bit was used to cut out the marked regions. The mask was then re-positioned over the face and, if requested by the participant, again removed to enable cutting away of any additional uncomfortable portions of the mask. In order to make the entire head immobilization assembly rigid, five strips of "Gorilla" tape with folded-over tabs to facilitate removal, were placed around the front frame of the head mask and attached to its back frame, gently squeezing the two frames together, thus immobilizing the head and neck. The entire assembly consisting of the collar and front and back masks was then removed from the participant, to be re-assembled and aligned (using the previously established felt-tip position markings on the Velcro strips) once the participant was placed onto the gurney of the fMRI scanner. There, a non-slip

plastic mesh mat was placed on the bottom of the head cradle, the participant, noise-attenuating ear plugs and head immobilization assembly in place, lay down supine in the Siemens Trio cradle and the 12-channel head cage cover with projection screen observation mirror was connected. The standard foam pads used to restrict head movement were then pressed in around the head immobilization assembly, and finally, the two foam-padded Siemens head cage adjustable clamps were pressed against the head-immobilization assembly, further preventing its movement.

2.1.4. Qualitative measurements

Each participant completed two open-ended interviews conducted by the author, as approved by the Institutional Review Board [please refer to Appendix C for Interview questions]. The pre-scan interview included questions about the participant's sexual and relationship histories, attitudes about sexuality, current sexual behaviors, and preferences regarding sexuality. This information will not be analyzed for this manuscript.

A post-scan interview was conducted to debrief the participant regarding her experience during the experiment. The participants were asked questions to establish their operational definitions of orgasm onset, termination, and recovery periods, i.e., what physical or cognitive cues informed them that their orgasm was beginning, ending, and when they had recovered post-orgasm back to baseline.

Information was also collected regarding how the scanner environment affected their experience. They were also asked to rate on a scale of 1 (low) to 7 (high) how aroused they were during the genital stimulation periods, how intense, pleasurable, and satisfying each orgasm was. Participants were asked whether they vocalized during the orgasm, experienced genital contractions, or ejaculated during orgasm. Participants were also asked to estimate the duration of their orgasm in seconds.

Additional information was collected but not analyzed for this manuscript regarding how the participants compared their self-induced and partner-induced orgasm experiences in the scanner.

2.1.5. Data analysis

All data were preprocessed and statistically analyzed using FMRIB's (Center for Functional Magnetic Resonance Imaging of the Brain, University of Oxford, UK) Software Library (FSL) version 6.00. Lower-level fMRI data processing was carried out using FMRI Expert Analysis Tool (FEAT).

Each participant's functional data were split into three files using FSLUTILS (fslroi) to create three separate data sets for analysis: (a) the physical stimulation/imagined stimulation conditions for use in Study 1: "Activation of sensory and other brain regions in response to imagined versus physical genital stimulation"; (b), the genital self-stimulation-induced orgasm condition, and (c), and the partner-stimulation-induced condition to be analyzed for Study 2: "Brain regional activation upon transition to self- and partner-induced orgasm in women:

an fMRI analysis".

Separate pre-processing and statistical analyses were performed for each data set. The following pre-processing steps were performed at the individual level: manual removal of skull and non-brain tissue from the anatomical and functional images.

For the analyses of both partner-stimulation induced and self-stimulation-induced orgasm conditions, FSL Motion Outliers was used to detect and remove time points corrupted by large motion. The resulting outlier file was added as a confound variable. In addition, standard motion parameters were added to the model. For the self-stimulation-induced orgasm condition, the group mean motion displacements were absolute = 1.48 mm, relative = 0.20. For the partner-stimulation-induced orgasm condition, the group mean motion displacements were absolute= 1.10 mm, relative = 0.18.

The data were spatially smoothed using a 5mm full-width at half-maximum Gaussian kernel (with the exception of the brainstem analysis in which the data were not spatially smoothed). Registration of the functional images to the high-resolution anatomical images was performed outside of the FEAT, using FLIRT (FMRIB's Linear Image Registration Tool), selecting the options: Mutual Information Cost Function and Sinc Interpolation (Blackman, width of Sinc Window= 7 voxels). Each participant's first level FEAT registration file was updated with the FLIRT registration conducted outside of FEAT prior to the higher-level analyses.

2.1.5.1. Self-induced orgasm compared with partner-induced orgasm

Fourteen experimental scanning sessions were conducted with the goal of acquiring within subject sets of partner-stimulation-induced and self-stimulation-induced orgasms that were counterbalanced. Ten participants were able to experience both conditions of orgasm during the course of the study. Six of those were in the partner-induced orgasm first protocol; four were in the self-stimulation-induced orgasm first protocol. Three additional participants in the self-stimulation-induced orgasm first protocol were able to experience the self-stimulation induced orgasm, but not the partner-stimulation-induced orgasm. After excluding one data set due to problems with the field-of-view, and one because of excessive head movement, we were unable to counterbalance the data for order effects as originally planned.

The preliminary t-tests in which self-stimulation orgasms that were experienced as the first orgasm of a scanning session were compared with self-stimulation-induced orgasms that followed another orgasm, suggested a significant order effect, as did the comparison of first and second partner-stimulation-induced orgasms. Thus we decided to use only “first” orgasms for the analysis: 5 self-stimulation-induced and 5 partner-stimulation-induced orgasms.

For both conditions of orgasm (self-stimulation-induced and partner-stimulation-induced), explanatory variables (EVs) were created at the first levels for early stimulation: the first 10 sec of stimulation; mid stimulation: the 10 sec of stimulation occurring during the middle of the participant’s stimulation epoch; late stimulation: the final 10 sec of stimulation prior to the onset of orgasm; orgasm:

the first 10 sec following the onset of orgasm; early recovery: the first 10 sec of the recovery period; and late recovery: the last 10 sec of the recovery period.

First level basic contrasts were set up for all EVs > 0 and < 0 (0 = global baseline). Differential contrasts were set up to compare each condition with the adjacent conditions: mid stimulation > early stimulation; early stimulation > mid stimulation; late stimulation > mid stimulation; mid stimulation > late stimulation; orgasm > late stimulation; late stimulation > orgasm; orgasm > early recovery; early recovery > orgasm; late recovery > early recovery; and early recovery > late recovery.

First level analyses were conducted with a high pass filter cutoff set at 100 sec. FILM (FMRIB's Improved Linear Model) prewhitening option was selected to improve estimation efficiency. The data was convolved using a Gaussian HRF with temporal derivatives. The EVs were used as regressors to determine the average activity elicited by each condition. The data at first level were corrected for multiple comparisons using a cluster-forming threshold of z=1.65 and a cluster-significance threshold of p = 0.05. The output files (contrast of parameter estimates, or “cope” files) were then used in the higher-level analysis to determine mean group effects and to perform contrast analyses between the conditions.

Higher-level analyses were performed using FMRIB’s Local Analysis of Mixed Effects (FLAME 1). A whole-brain analysis was conducted in which the FEAT files containing all basic and differential contrasts from the first levels were passed up to the higher-level analysis. A two-group unpaired t-test was

conducted with EV 1= Self-stimulation-induced orgasm inputs, and EV 2 = partner-stimulation orgasm inputs. Contrasts were set up for self-induced orgasm group means, partner-induced orgasm group means, self-induced orgasm group > partner-induced orgasm group, and partner-induced orgasm group > self-induced orgasm group.

Two additional group analyses were conducted as above, but with specific regions of interest. One analysis masked the frontal lobe, the other, the temporal lobe in order to determine if there were any deactivations (activity significantly lower than the global baseline) in these specific regions.

All group results were corrected for multiple comparisons with a cluster-forming threshold set at $z = 1.65$, $p < 0.05$.

2.1.5.2. Combined self- and partner-induced orgasm

Results of first levels for the self-stimulation-induced orgasm group and partner-stimulation-induced orgasm group were combined by passing up the respective FEAT files to the higher level group analysis, using a single group average to create the combined orgasm group.

A differential contrast that was not conducted on the first levels, orgasm > mid stimulation, was created by entering the first level COPE files for the basic contrasts, orgasm > 0 and mid stimulation > 0, and conducting a paired t-test between the two conditions. Two differential contrasts were created, middle stimulation > orgasm and orgasm > mid stimulation.

Two additional group analyses targeting the frontal and temporal lobes,

respectively, were conducted for the combined orgasm group as was done for each of the groups separately in order to determine if there were any deactivations (activity significantly lower than the global baseline) in these regions of interest observed for the basic contrasts.

All group results were corrected for multiple comparisons with a cluster-forming threshold set at $z = 1.65$, $p = 0.05$, with the exception of additional contrasts ran for the orgasm > late stimulation, which were thresholded at $z = 1.55$ $p < 0.01$, and the brainstem analyses which were thresholded at $z = 1.0$, $p < 0.01$.

2.1.5.3. Time-course analysis

The regions of interest for the time course analysis of the combined orgasm data were selected based on the significantly active regions found in the following differential contrasts: mid stimulation > early stimulation, orgasm > mid stimulation, orgasm > late stimulation, orgasm > early recovery, and early recovery > late recovery. Masks were created for the brainstem, the secondary somatosensory cortex (combined bilateral regions OP 1-4), cerebellum, insula, paracentral lobule, frontal cortex, hypothalamus, left and right amygdala, left and right nucleus accumbens, and left and right hippocampus. The 13 masks were converted from standard space to each individual's native space. For each participant and each region, the time-series was extracted from the temporally high-pass filtered and motion-corrected "filtered functional "data file for 11 TRs centered on the "onset" of orgasm -- encompassing the 10 sec immediately

before and the 10 sec immediately after, orgasm onset. The output text files containing the time-course values were moved to MS Excel for a group calculation of TR by TR (2 sec) comparison of the percent change from a 60 sec resting baseline.

2.2. Results [Please refer to Appendix H for summary of results]

2.2.1. Brain regions activated during genital stimulation, orgasm, and recovery

2.2.1.1. Self- vs. partner-induced orgasm

In comparing the self and partner stimulation groups, there were no significant differences in *activations* between groups during orgasm contrasts (orgasm > mid stimulation; orgasm > late stimulation; and orgasm > early recovery) for frontal or any other brain region. [Please refer to Appendix E: Additional orgasm results].

Furthermore, there were no significant *deactivations* in either self- or partner-stimulation groups, or when partner and self groups were combined, for the basic contrast orgasm < 0 when region of interest (ROI) analyses were conducted separately for the frontal and temporal lobes (using the criterion of cluster $z = 1.5$, $p < 0.05$).

Another way to ascertain if there were regions that had lower activity during orgasm than in the periods immediately before, (late stimulation) or after (early recovery), was to explore the results of the differential contrasts, late stimulation > orgasm and early recovery > orgasm. However, neither were there

any significant results for these contrasts for the self group, partner group, or combined self and partner group.

The only significant group differences occurred during pre-orgasm stimulation, with the self-stimulation group having significantly more activity in the contrast, mid-stimulation > early stimulation. The regions significantly more active in the self-stimulation group included sensory integration regions, the parietal operculum and right insula, the dorsal striatum (bilateral caudate and right putamen), bilateral amygdala, and the medial prefrontal and anterior cingulate cortex.

Conversely, the partner-stimulation group had significantly more activity during the contrast, late stimulation > mid stimulation in the following regions: the genital sensory cortex (paracentral lobule), the secondary somatosensory cortex (regions OP1 and OP4, right), right thalamus; right insula, right hippocampus, the posterior cingulate cortex, bilateral putamen, premotor cortex, and the medial prefrontal cortex [See Appendix E: Additional orgasm results].

There were no significant group differences for the recovery contrasts. [Please refer to Appendix E: Additional orgasm results].

2.2.1.2. Combined self- and partner-induced orgasm

Based on the overall lack of significant differences between self and partner groups, we combined the two groups.

There were widespread activations observed in multiple brain regions, with different patterns related to the different phases of stimulation, orgasm, and

recovery, including primary sensory, motor, sensory-integration, and reward regions. More specifically, these regions included the prefrontal cortex, paracentral lobule (genital sensory cortex), secondary somatosensory cortex (operculum, SII), parietal cortex, insula, anterior cingulate cortex, posterior cingulate cortex, hippocampus, amygdala, ventral tegmentum, nucleus accumbens, cerebellum, caudate and hypothalamus.

Results showing additional regions that were activated during the course of stimulation, orgasm, and recovery, i.e. the primary motor cortex, supplementary motor area, thalamus, visual cortex, and temporal pole are presented in Appendix E: Additional orgasm results.

First, a summary of the results will be reviewed for the following operationally defined periods of the "orgasm sequence": (1) sexual arousal (mid stimulation > early stimulation), (2) orgasm greater than sexual arousal (orgasm > mid stimulation), (3) orgasm greater than the end of orgasm (orgasm > early recovery), and (4) activity that persists post orgasm, decreasing over the course of recovery (early recovery > late recovery).

The results of the period of "going over " into orgasm, i.e., the first 10 sec of orgasm greater than the last 10 sec of stimulation (orgasm > late stimulation) will be presented in a following section.

A) Prefrontal Cortex

A pattern of increased activity in the prefrontal cortex (Figure 1) was observed over the course of genital stimulation (mid-stimulation > early stimulation), increasing at orgasm (orgasm > mid stimulation, orgasm > early recovery), and decreasing during the course of recovery (early recovery > late recovery).

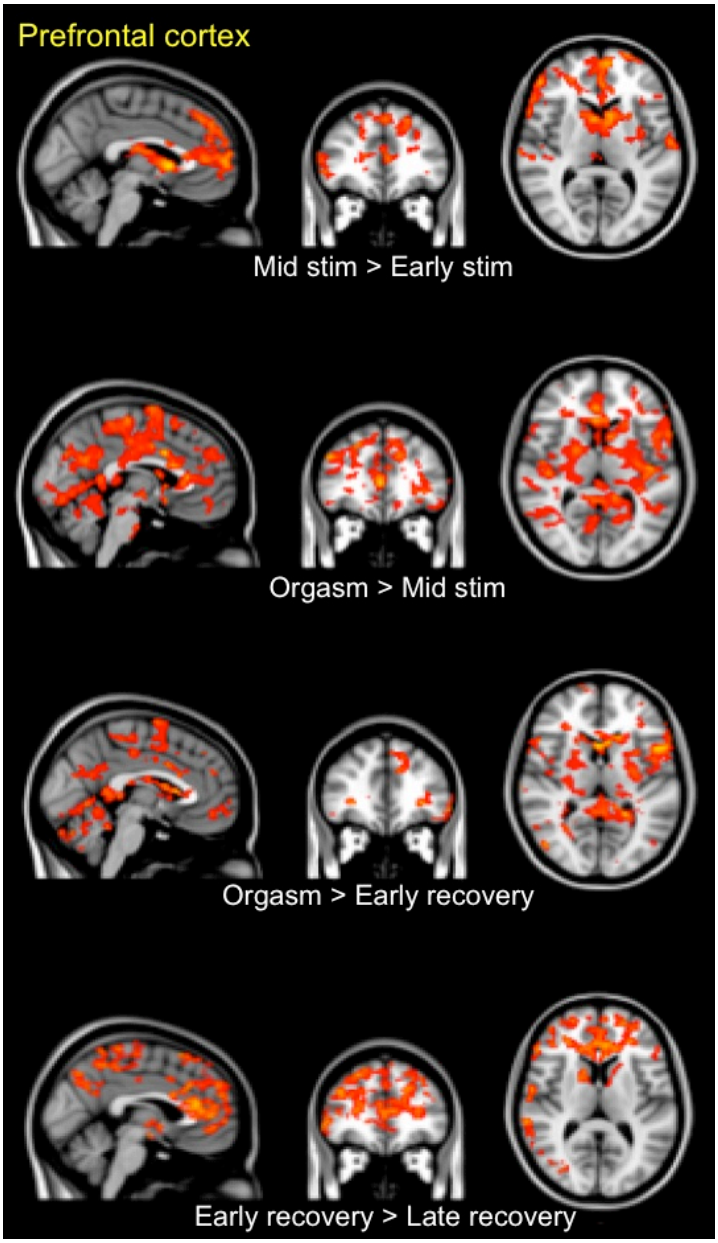


Figure 1. Prefrontal cortical activity increased during the course of genital stimulation and orgasm. Combined group; Flame 1, Cluster 1.65, $p < 0.05$.

B) Paracentral lobule

Activation of the mesial paracentral lobule (the genital sensory cortex) increased as stimulation led up to orgasm (orgasm > mid stimulation; orgasm> early recovery), and decreased during the course of recovery (Figure 2).

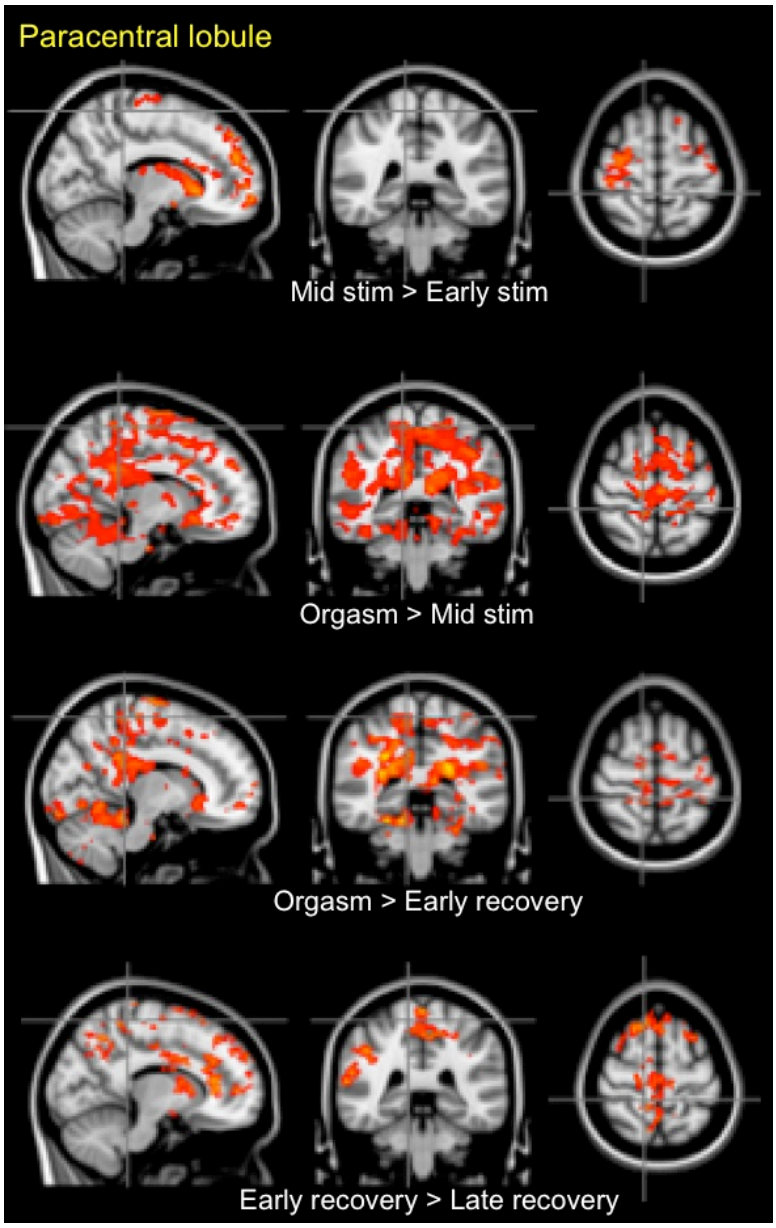


Figure 2. Paracentral lobule (genital sensory cortex): activation during the orgasm sequence. Combined group; Flame 1, Cluster 1.65, $p < 0.05$.

C) Operculum- S II

The secondary somatosensory cortex became active at orgasm compared to the periods of mid-stimulation and early recovery, with slight activity persisting into the recovery period (Figure 3).

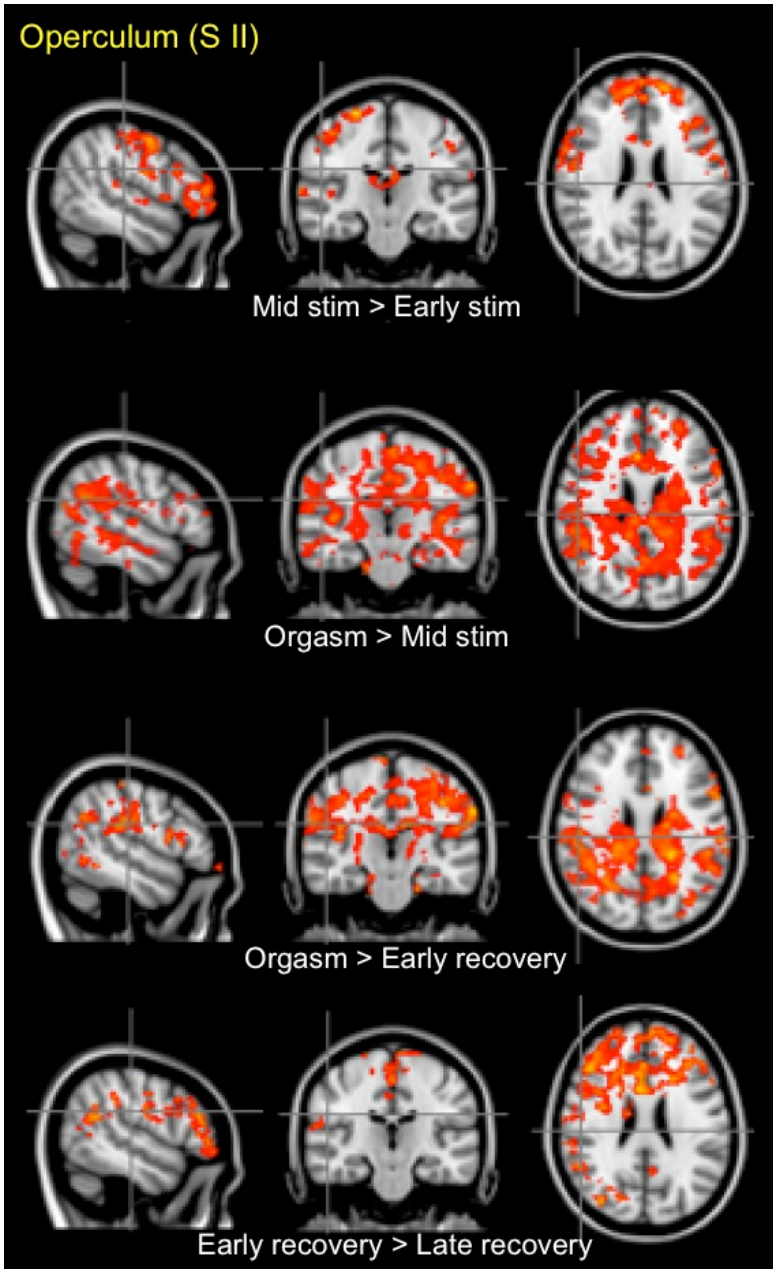


Figure 3. Parietal operculum (S11): secondary somatosensory cortex activity during the orgasm sequence. Combined group; Flame 1, Cluster 1.65, $p < 0.05$.

D) Parietal cortex

As observed in Figure 4, the parietal cortex, in the region of the precuneus, was increasingly activated during the orgasm sequence, with this activity decreasing over the course of the recovery period.

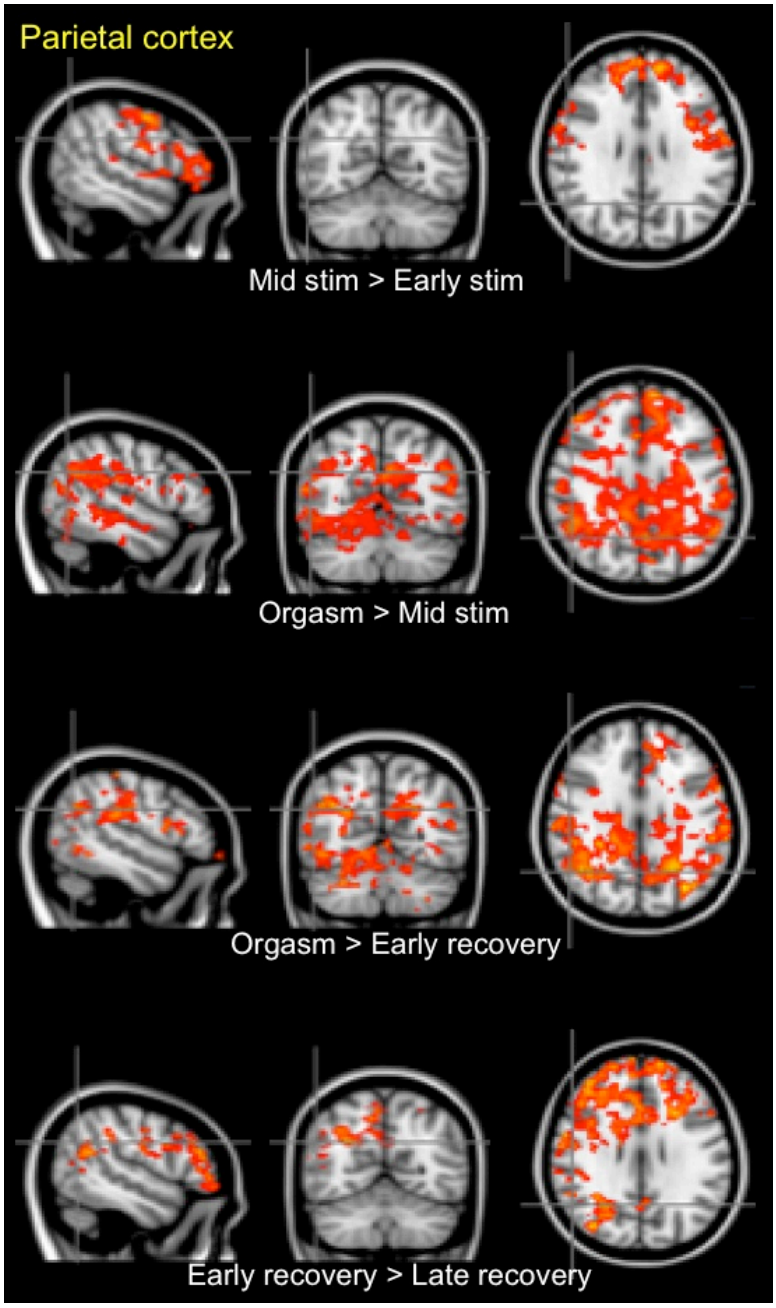


Figure 4. Parietal cortical activity during the orgasm sequence. Combined group; Flame 1, Cluster 1.65, $p < 0.05$.

E) Posterior Insula

The posterior insula became active during the orgasm sequence, with this activity extinguishing by the end of recovery (Figure 5).

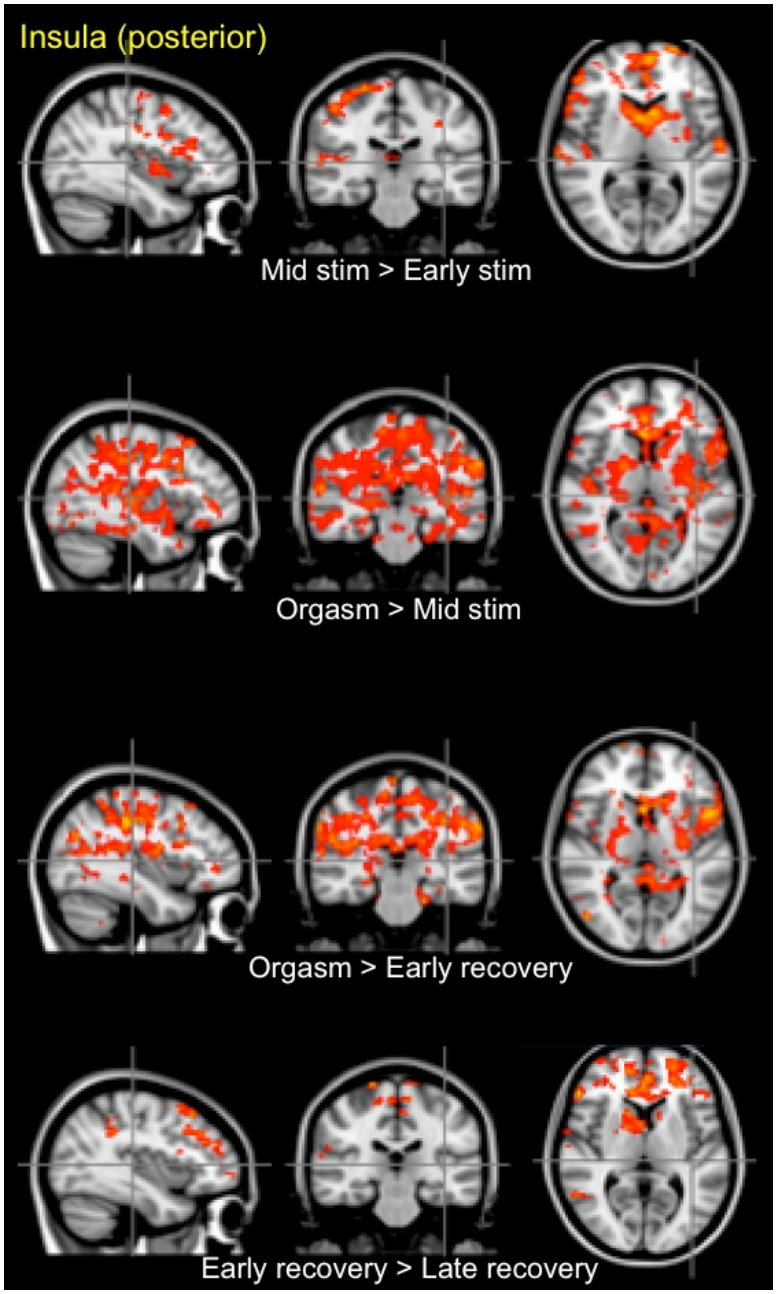


Figure 5. Increased posterior insula activation during the stimulation to orgasm sequence. Combined group; Flame 1, Cluster 1.65, $p < 0.05$.

F) Anterior cingulate cortex

The anterior cingulate cortex became active during sexual arousal, and increased in activation during orgasm, compared to both mid-stimulation and early recovery. It was still active in early recovery compared to late recovery (Figure 6). The posterior cingulate cortex (Figure 7), similarly, was activated at orgasm compared to both mid-stimulation and early recovery.

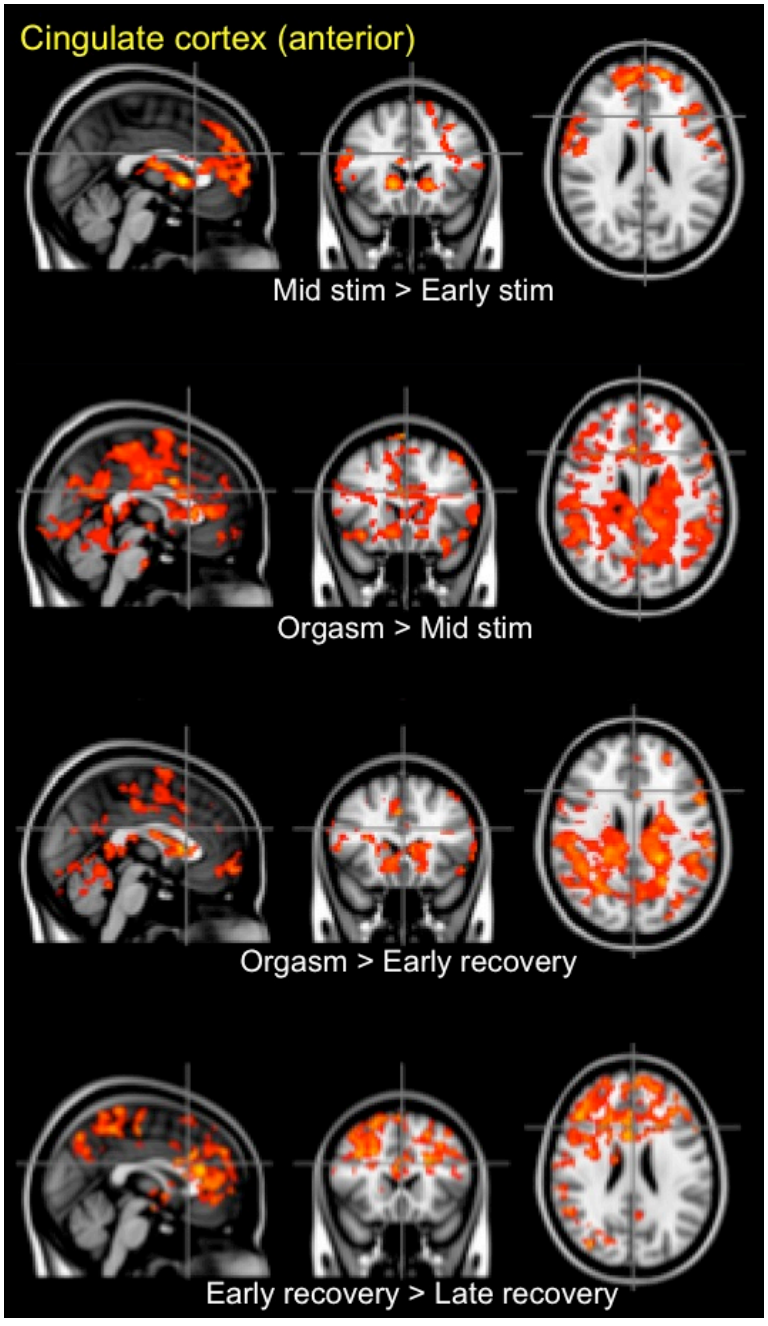


Figure 6. Activation of the anterior cingulate cortex throughout the orgasm sequence. Combined group; Flame 1, Cluster 1.65, $p < 0.05$.

G) Posterior cingulate cortex

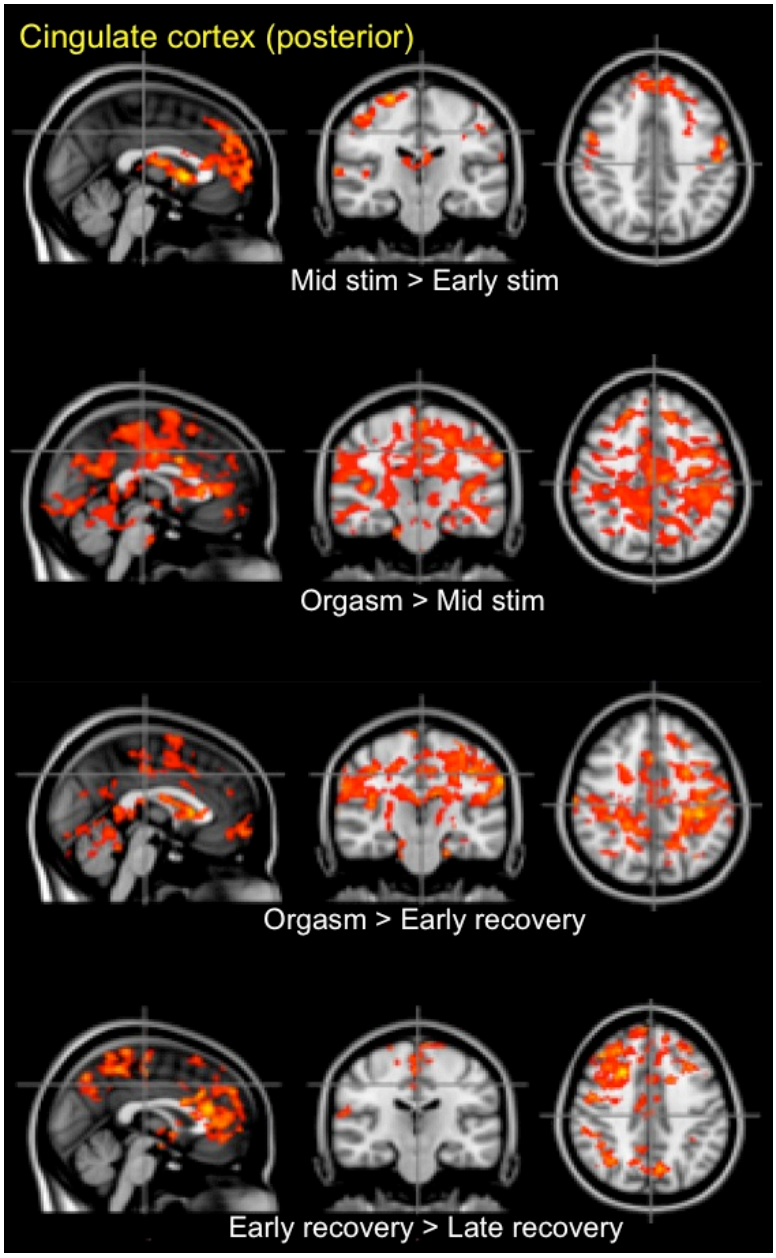


Figure 7. Posterior cingulate activation at orgasm compared with mid stimulation and early recovery. Combined group; Flame 1, Cluster 1.65, $p < 0.05$.

H) Hippocampus

The right hippocampus was active during sexual arousal (mid-stimulation > early stimulation), and bilaterally activated at orgasm (compared with mid-stimulation); but not activated when orgasm was compared to early recovery (Figure 8).

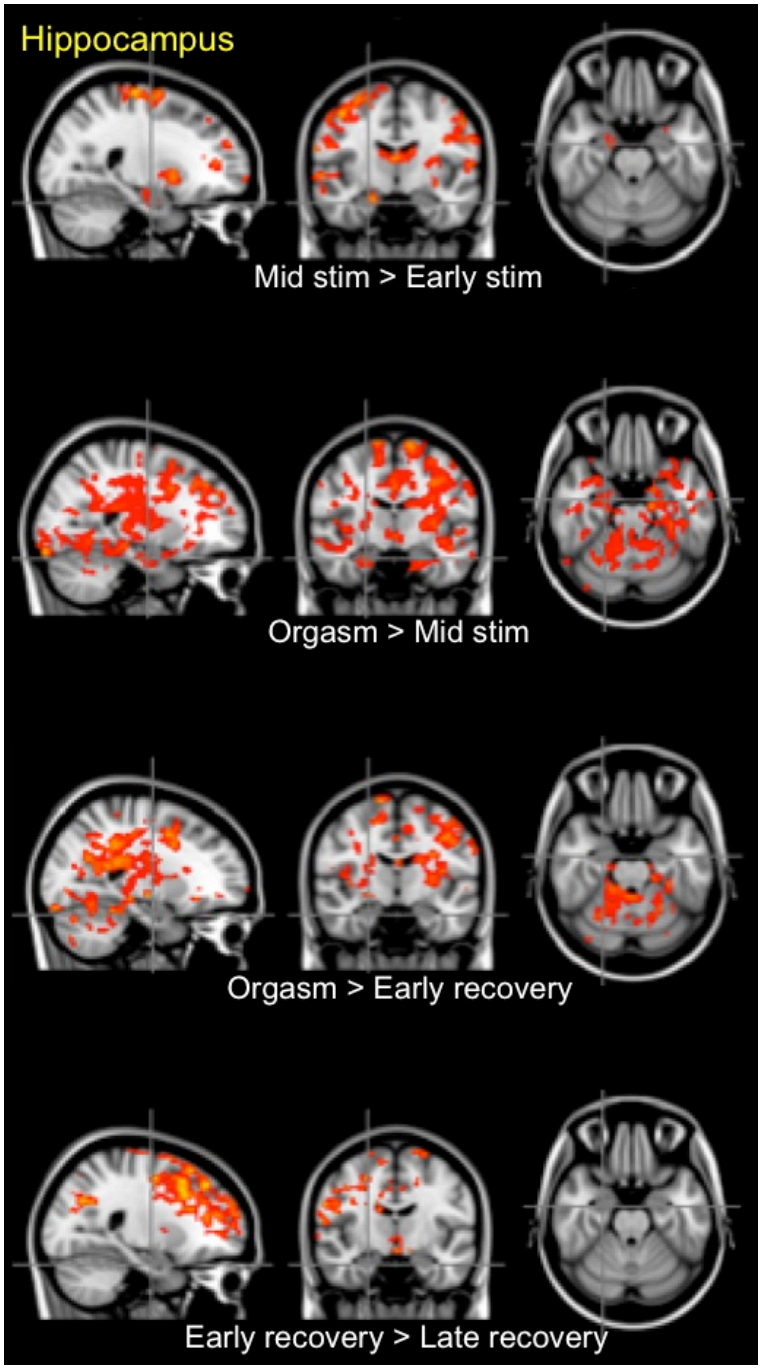


Figure 8. Hippocampus activation during sexual arousal and orgasm compared to mid stimulation. Combined group; Flame 1, Cluster 1.65, $p < 0.05$.

I) Amygdala

Similar to the pattern observed for the hippocampus, the amygdala was activated during sexual arousal, and bilaterally activated during orgasm compared to mid-stimulation, but not at orgasm compared to early recovery (Figure 9).

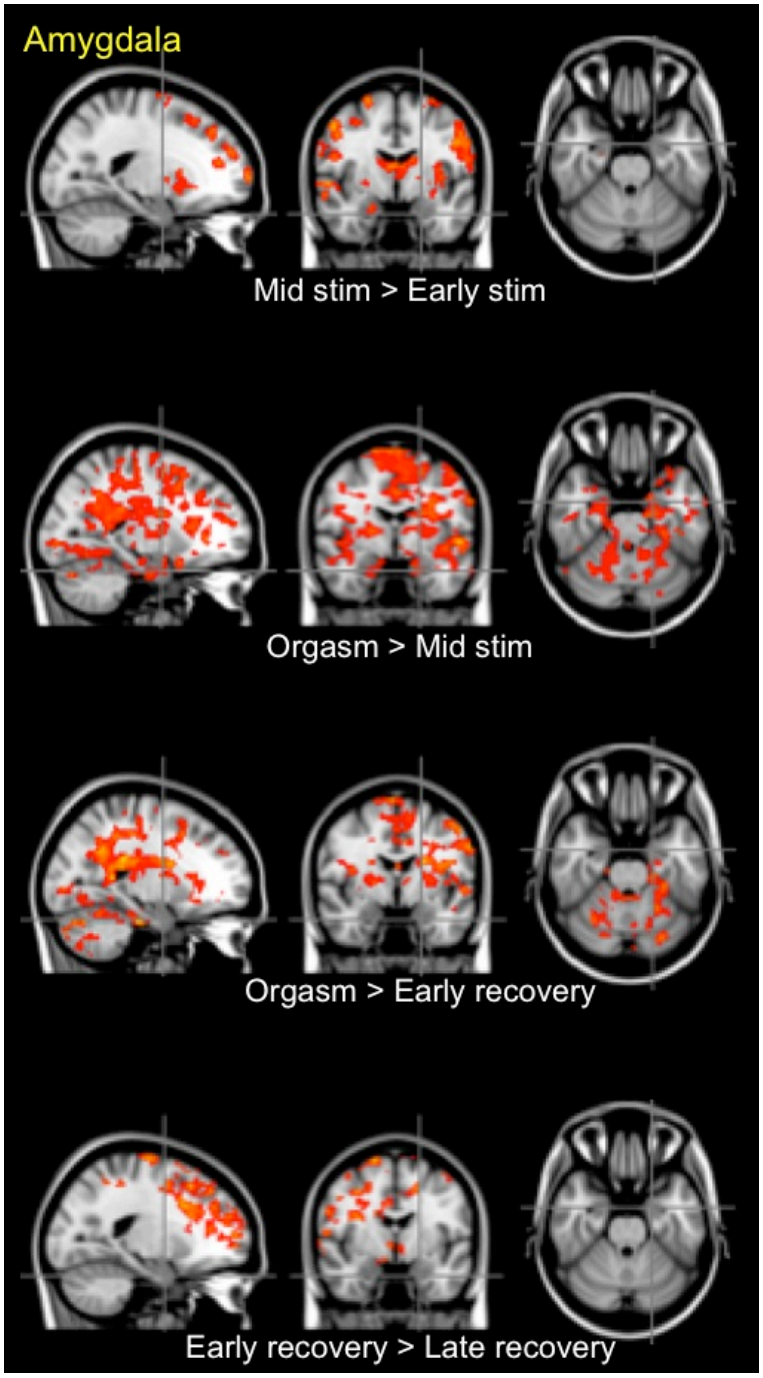


Figure 9. Amygdala activated during sexual arousal and orgasm. Combined group; Flame 1, Cluster 1.65, p <0.05

J) Ventral tegmentum

The ventral tegmentum was only activated at orgasm compared to mid-stimulation (Figure 10). However, the nucleus accumbens (Figure 11) was bilaterally activated during sexual arousal and orgasm compared to mid-stimulation.

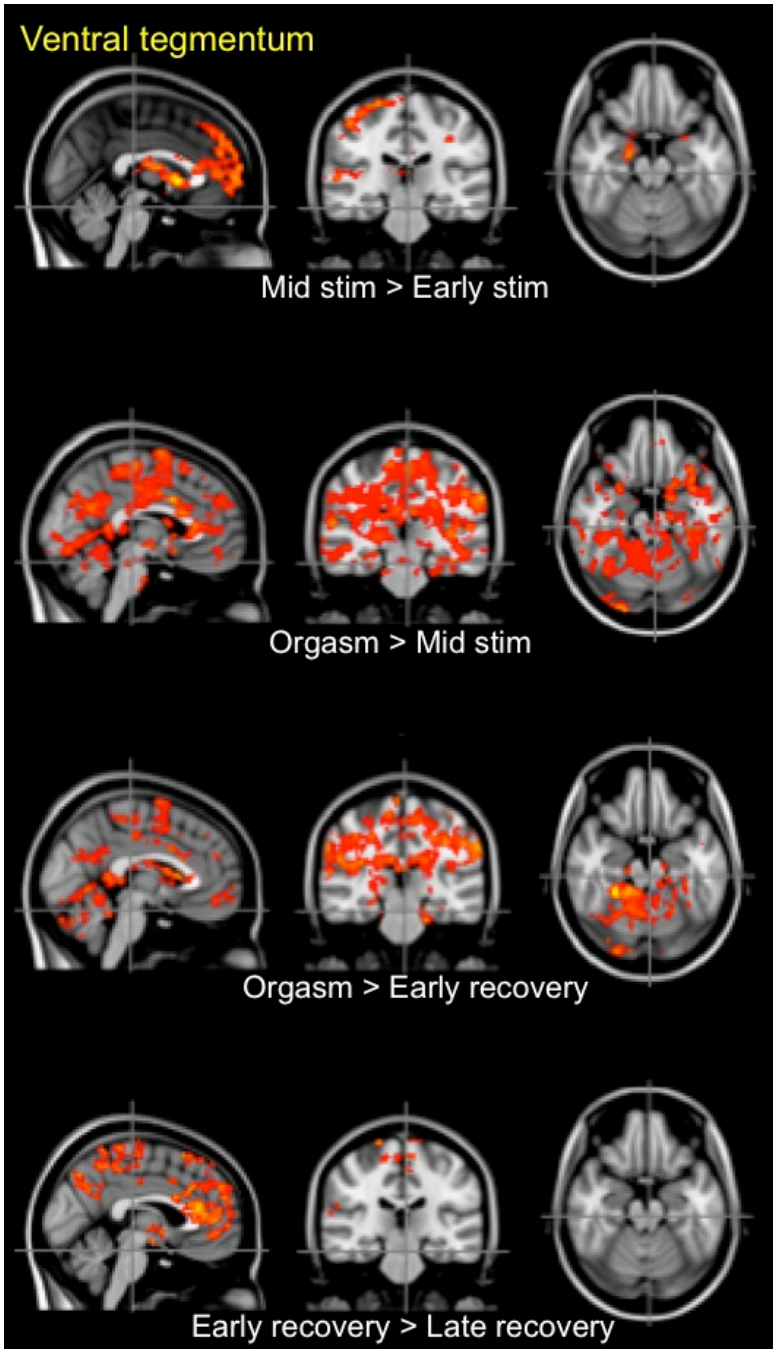


Figure 10. Ventral tegmentum activated at orgasm compared to mid-stimulation. Combined group; Flame 1, Cluster 1.65, $p < 0.05$.

K) Nucleus accumbens

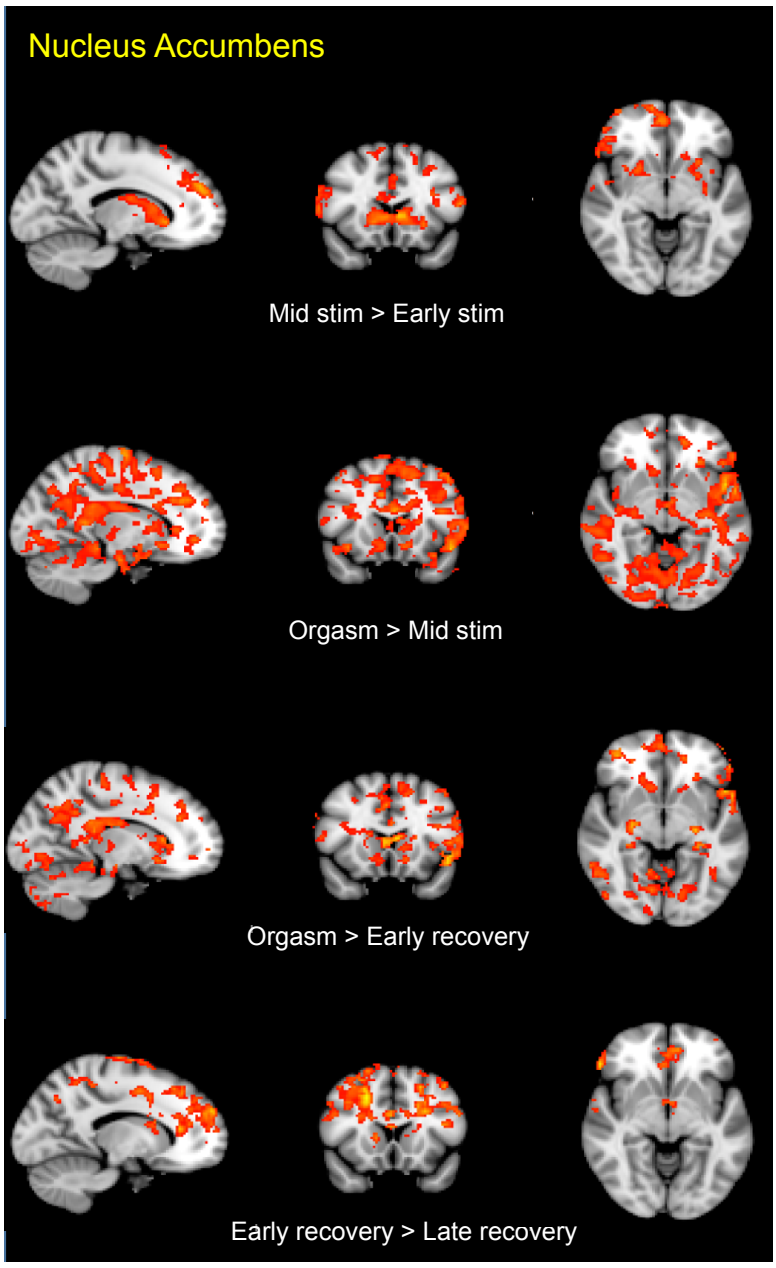


Figure 11. Nucleus accumbens activated during arousal and orgasm (compared to mid stimulation). Combined group; Flame 1, Cluster 1.65, p <0.05.

L) Cerebellum

The cerebellum was activated during orgasm compared to mid-stimulation and early recovery (Figure 12).

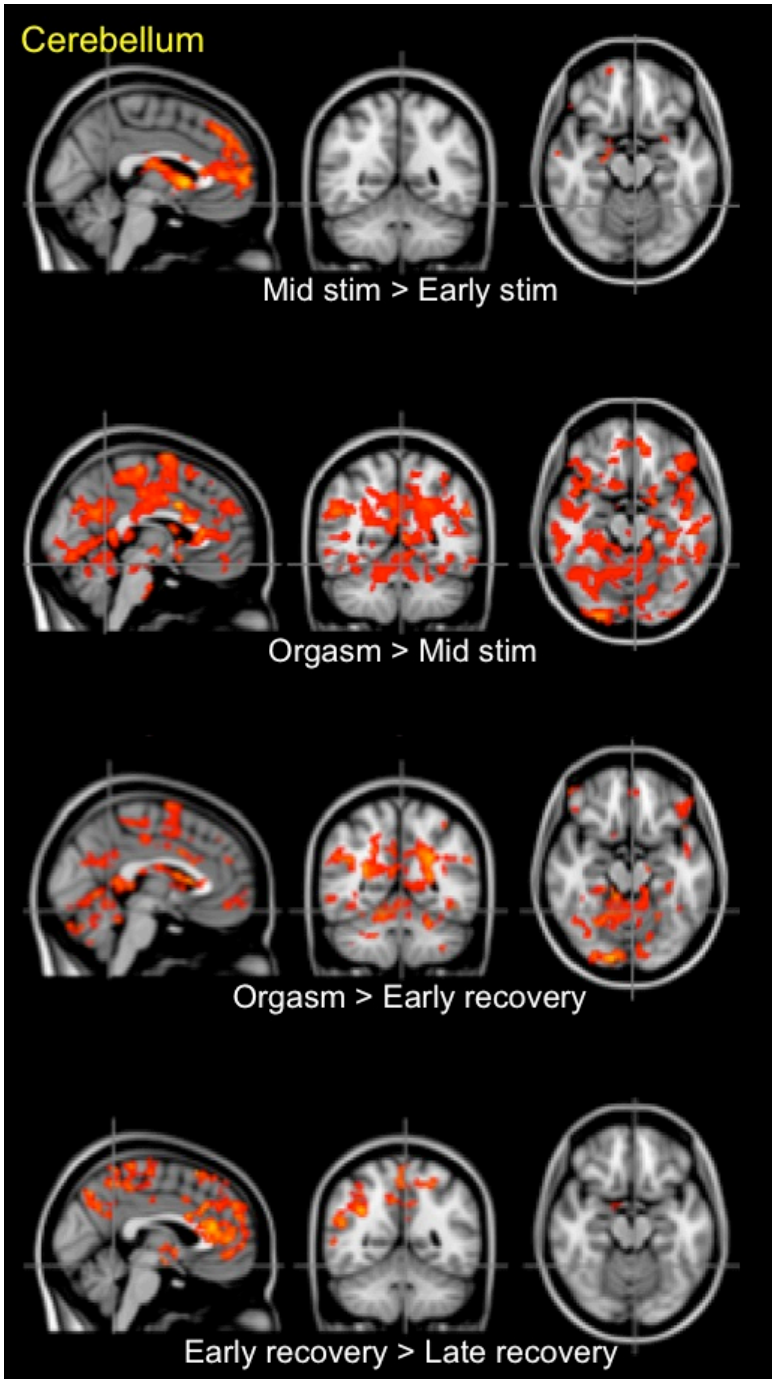


Figure 12. Cerebellum activated during orgasm. Combined group; Flame 1, Cluster 1.65, p <0.05.

M) Caudate

The caudate was activated bilaterally during genital stimulation and orgasm compared to mid stimulation; and activated on the left side during orgasm compared to early stimulation (Figures 13-15).

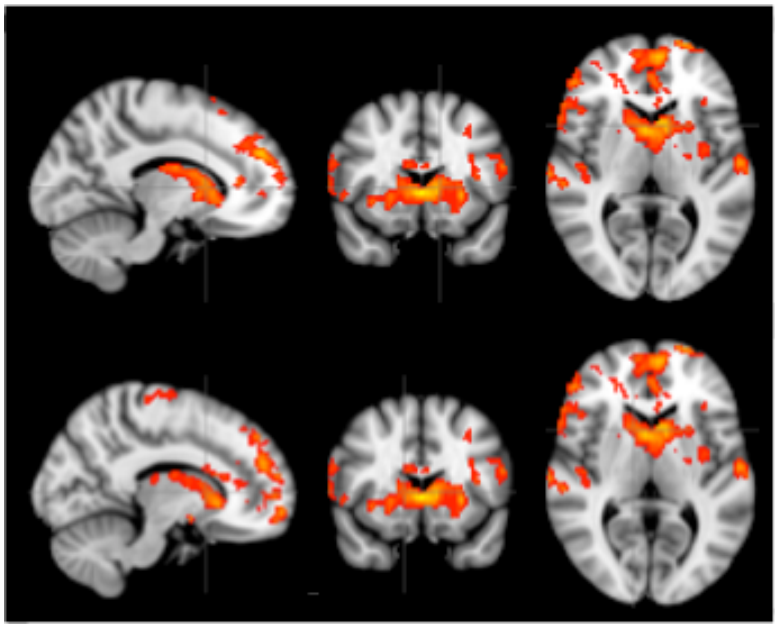


Figure 13. Bilateral caudate activity greater during mid-stimulation than early stimulation. Combined group; Flame 1, Cluster 1.65, $p < 0.05$. Top: Left caudate. Bottom: Right caudate

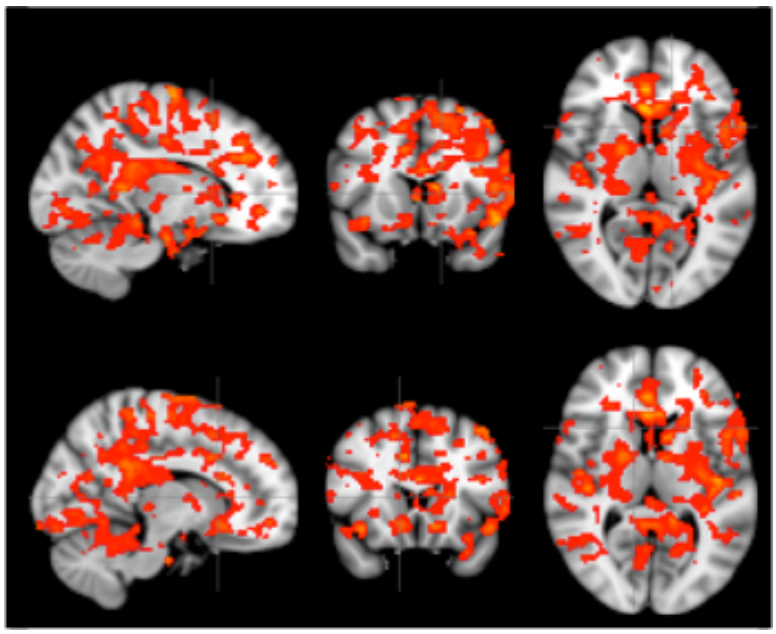


Figure 14. Bilateral caudate activity greater during orgasm than mid-stimulation. Combined group; Flame 1, Cluster 1.65, $p < 0.05$. Top: Left caudate. Bottom: Right caudate.

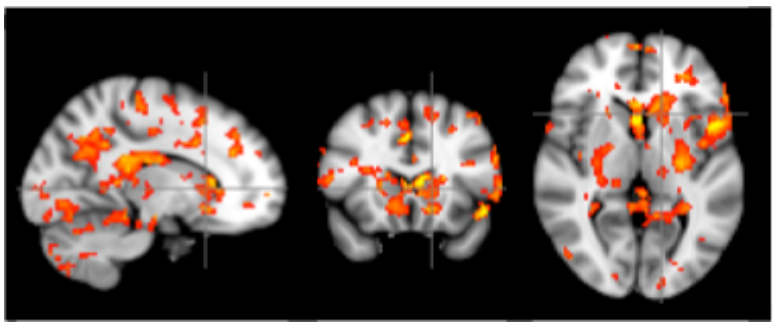


Figure 15. Left caudate activity during orgasm compared to early recovery. Combined group; Flame 1, Cluster 1.65, p <0.05.

N) Hypothalamus

Hypothalamic activations were observed (Figures 16 and 17) during sexual arousal (mid stimulation > early stimulation) and recovery (early recovery > late recovery). Evidence of hypothalamic activity during the "going over" into orgasm sequence (orgasm > late stimulation) will be presented in the results for the brainstem ROI analysis.

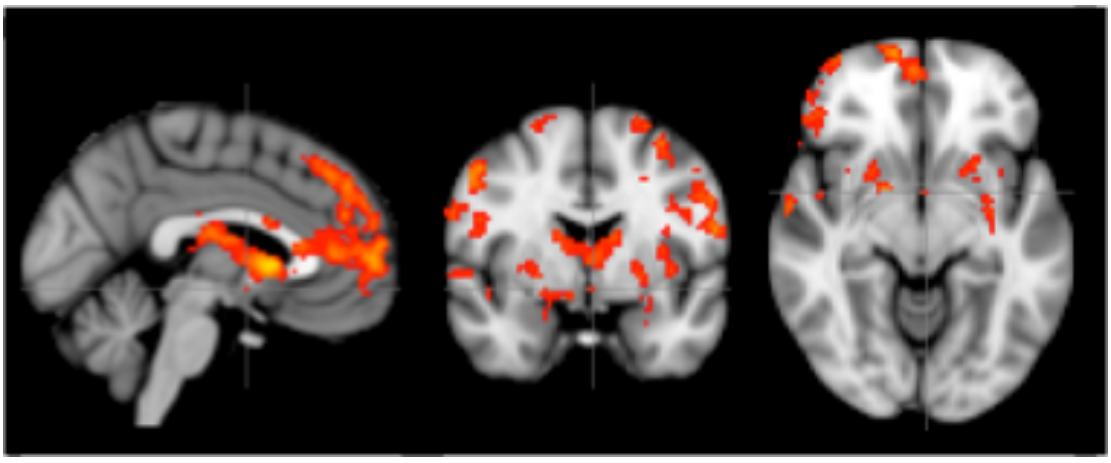


Figure 16. Hypothalamus activity during sexual arousal (mid stimulation > early stimulation). Combined group; Flame 1, Cluster 1.65, p <0.05.

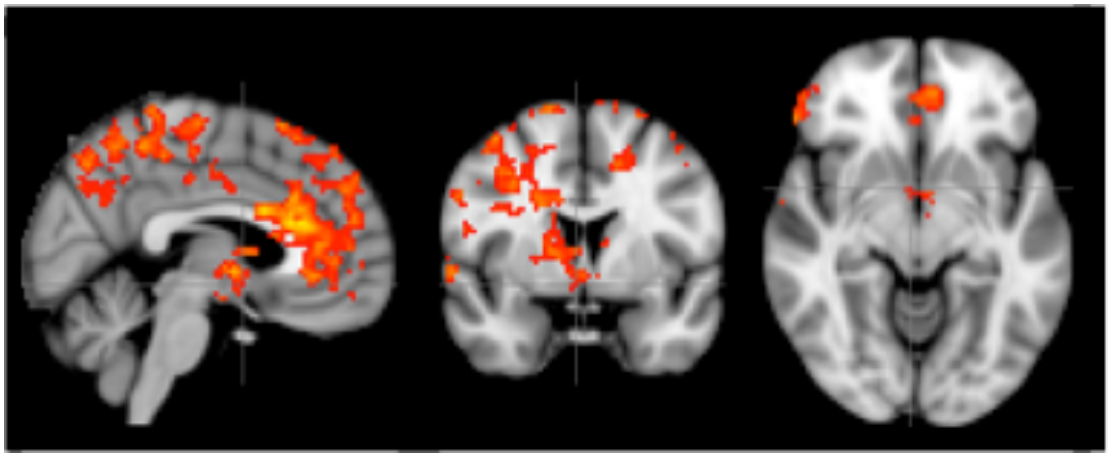


Figure 17. Hypothalamic activity during recovery period, post-orgasm (early recovery > late recovery). Combined group; Flame 1, Cluster 1.65, $p < 0.05$.

2.2.2. Significant activations at the transition: Orgasm > late stimulation

As shown in Figure 18, “going over” to orgasm, operationally defined as the first 10 sec of orgasm > last 10 sec of stimulation (i.e., immediately preceding orgasm), showed activation of the genital sensory cortex (paracentral lobule), bilateral activation of the operculum (secondary somatosensory cortex: “SII”, OP 1 left and OP4 right), the left insula, posterior cingulate, the precuneus region of the parietal cortex, and the inferior parietal lobe.

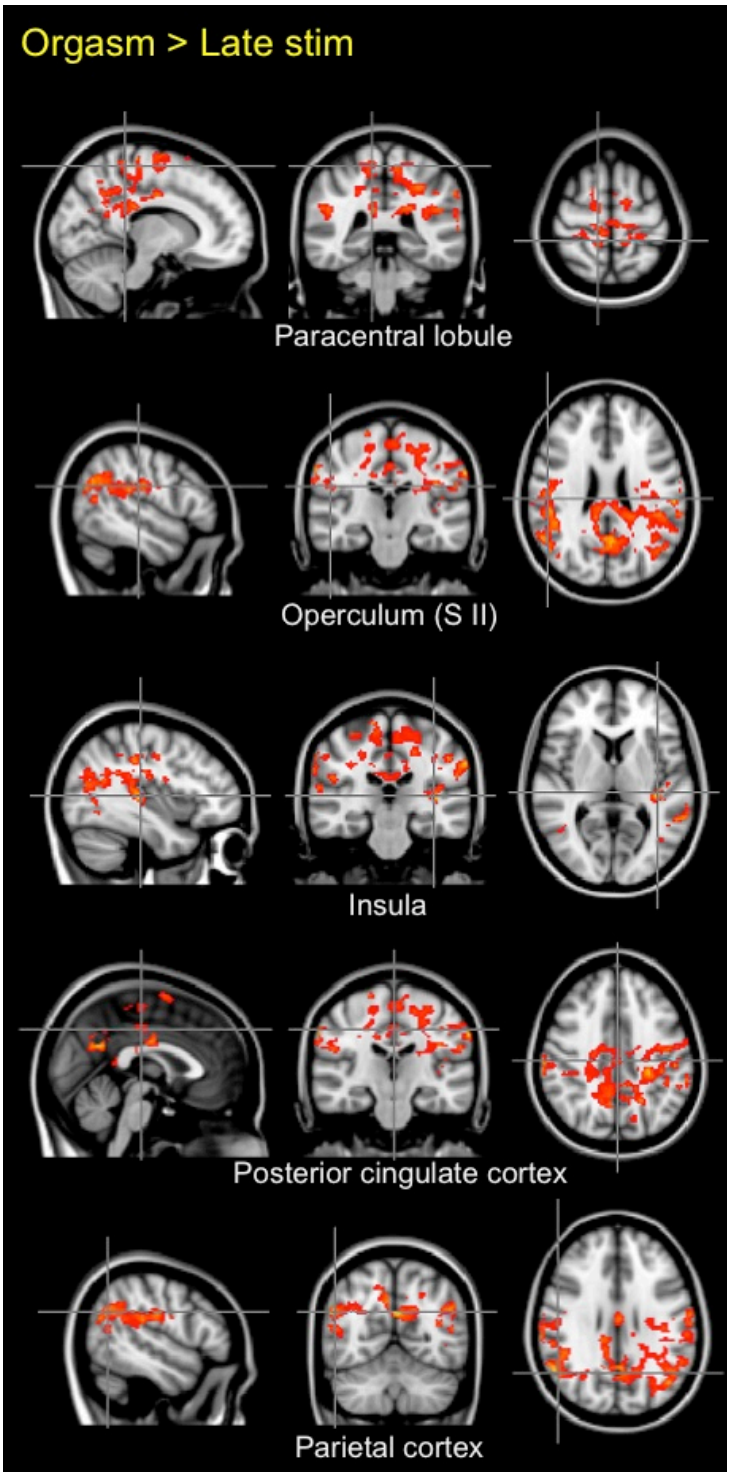


Figure 18. Regional activation associated with orgasm compared to late stimulation. Combined group; Flame 1, Cluster 1.65, $p < 0.05$.

For the contrast, orgasm > late stimulation, lowering the cluster-forming threshold from 1.65 to 1.5, p < 0 .01 resulted in additional regions of activation for the right hippocampus (Figure 19), bilateral amygdala (Figure 20), right nucleus accumbens and septum (Figure 21), and the anterior hypothalamus (Figure 22).

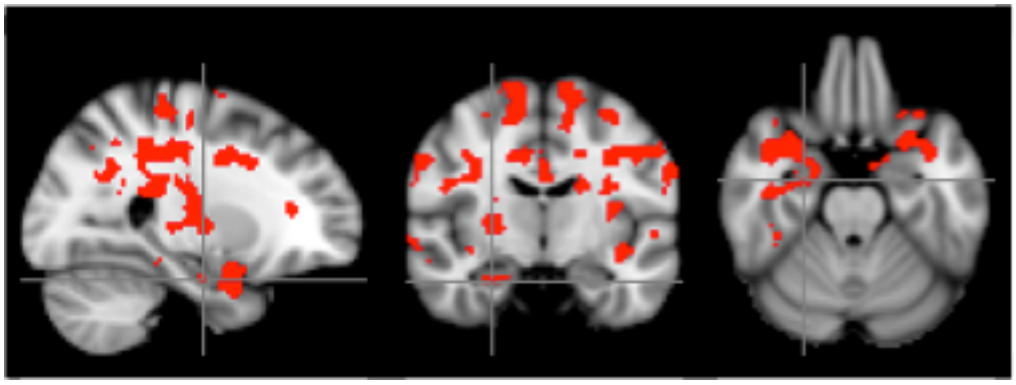


Figure 19. Right hippocampus activation at orgasm compared to late stimulation. Combined group; Flame 1, Cluster 1.5, p <0.01.

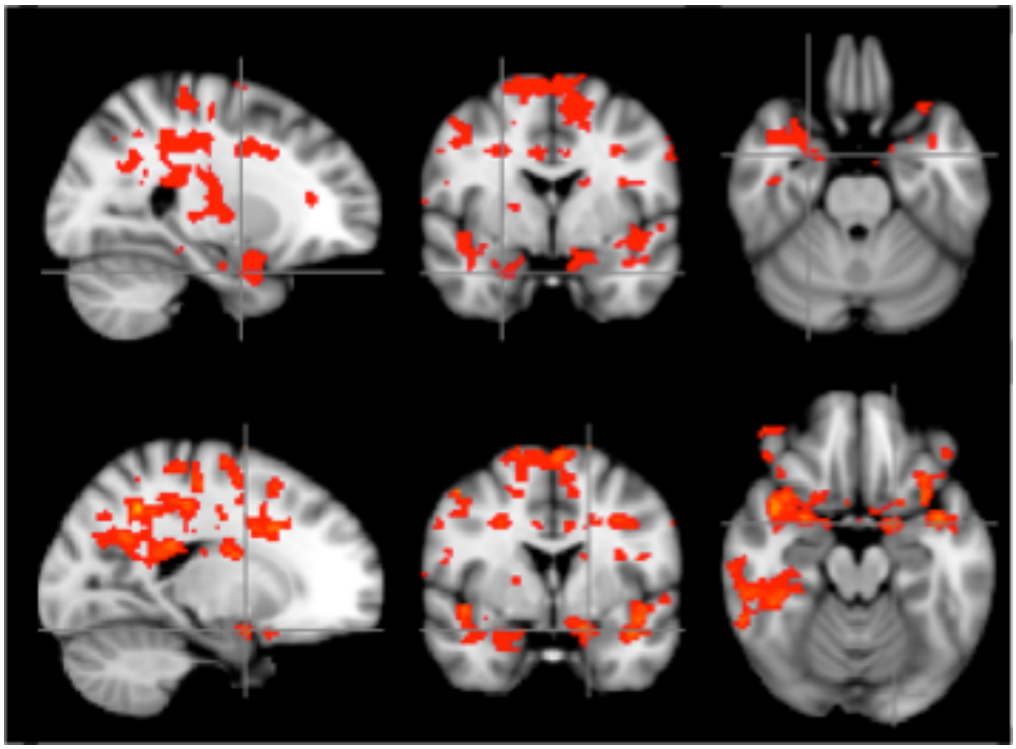


Figure 20. Right amygdala (top) and left amygdala (bottom) activation at orgasm greater than late stimulation. Combined group; Flame 1, Cluster 1.5, p <0.01.

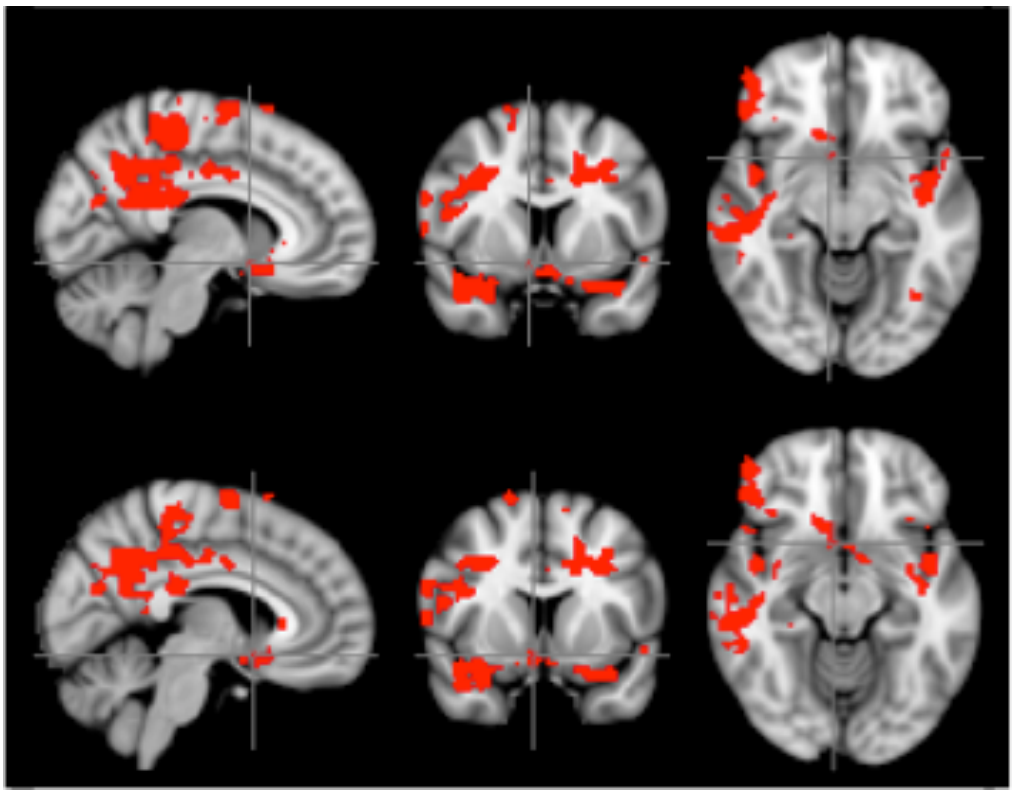


Figure 21. Activation greater at orgasm than late stimulation. Top: Right nucleus accumbens activity. Bottom: Septum. Combined group; Flame 1, Cluster 1.5, p <0.01.

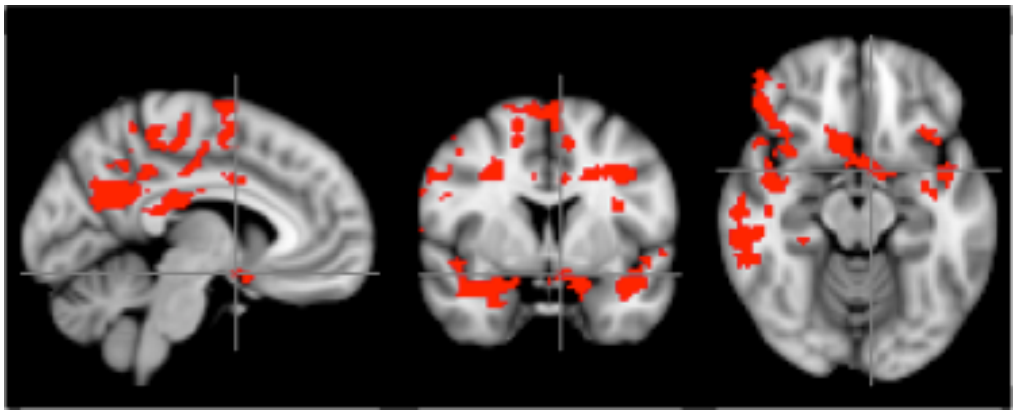


Figure 22. Anterior hypothalamus activated at orgasm compared to late stimulation. Combined group; Flame 1, Cluster 1.5, p <0.01.

In the analysis of the brainstem activity Orgasm > Late stimulation (i.e., the first 10 sec of orgasm > 10 sec of stimulation immediately preceding orgasm onset), the regions include the posterior hypothalamus and periaqueductal gray (Figure 23), lower brainstem dorsal raphe and vagus nuclei (Figure 24), the ventral tegmentum and substantia nigra (Figure 25), and the pontine mesencephalic trigeminal nucleus (Figure 26).

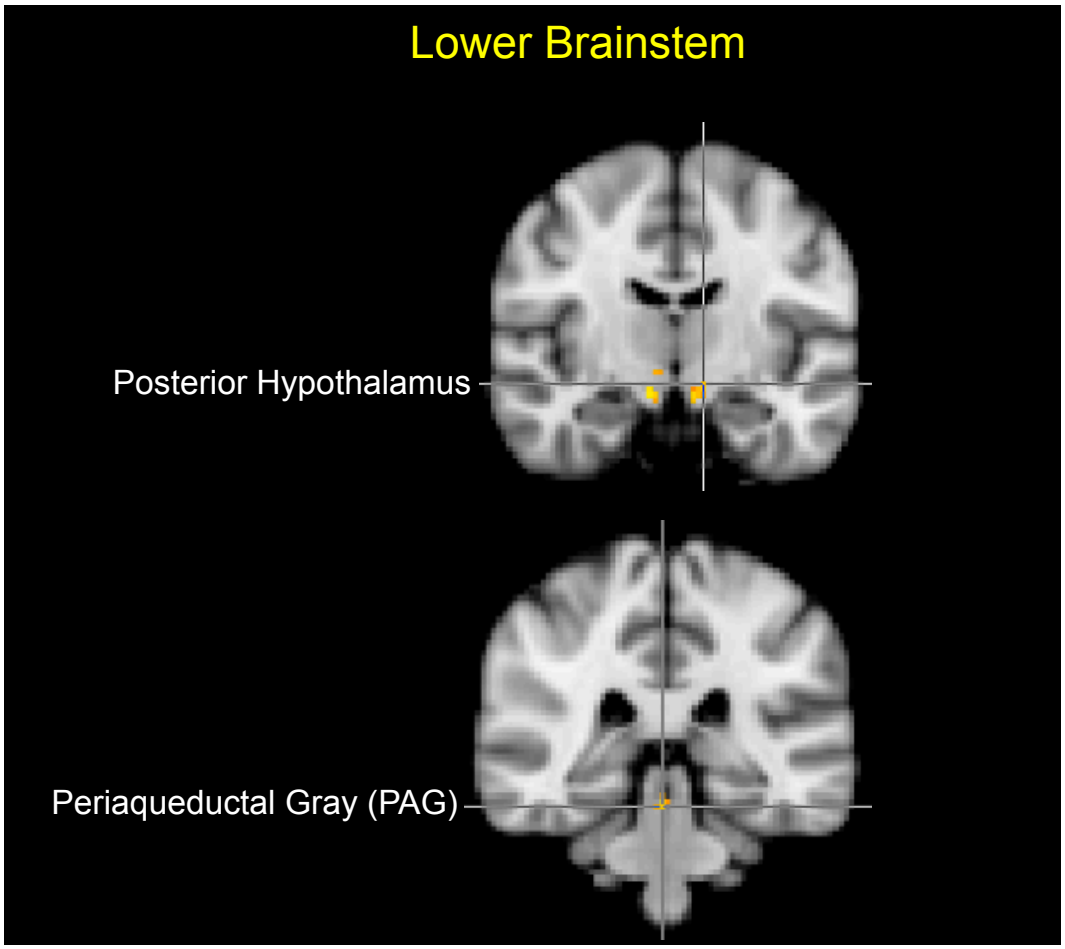


Figure 23. Posterior hypothalamus and periaqueductal gray activated at orgasm compared to late stimulation. Combined group; Flame 1, Cluster 1.5, p <0.01.

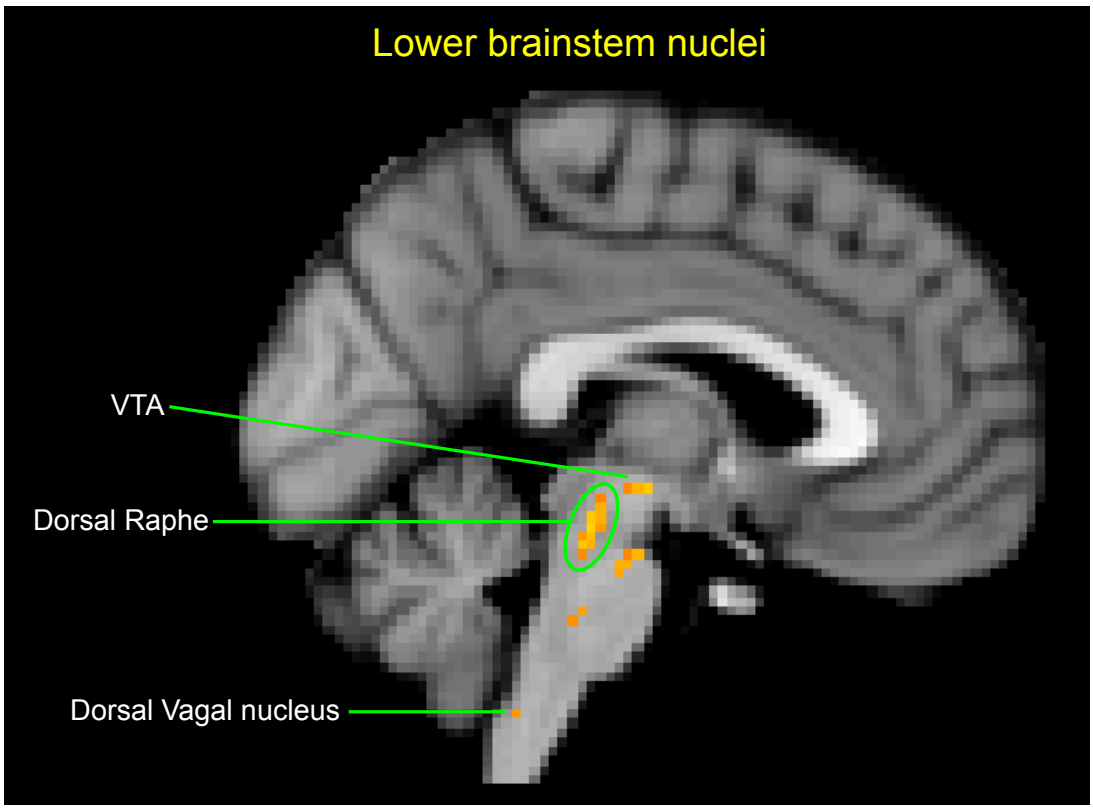


Figure 24. Lower brainstem dorsal raphe and dorsal vagal nuclei activated at orgasm compared to late stimulation. Combined group; Flame 1, Cluster 1.0, p <0.01.

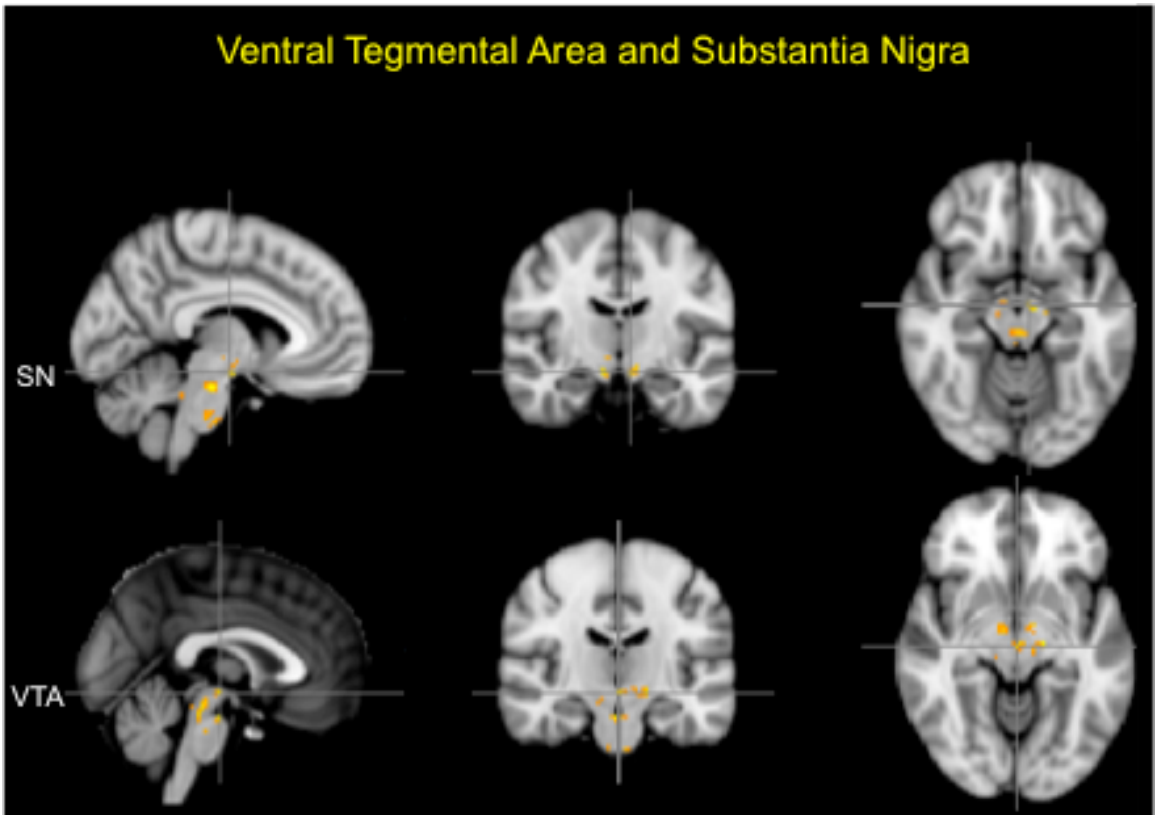


Figure 25. Ventral tegmentum and substantia nigra activated at orgasm compared to late stimulation. Combined group; Flame 1, Cluster 1.0, p <0.01.

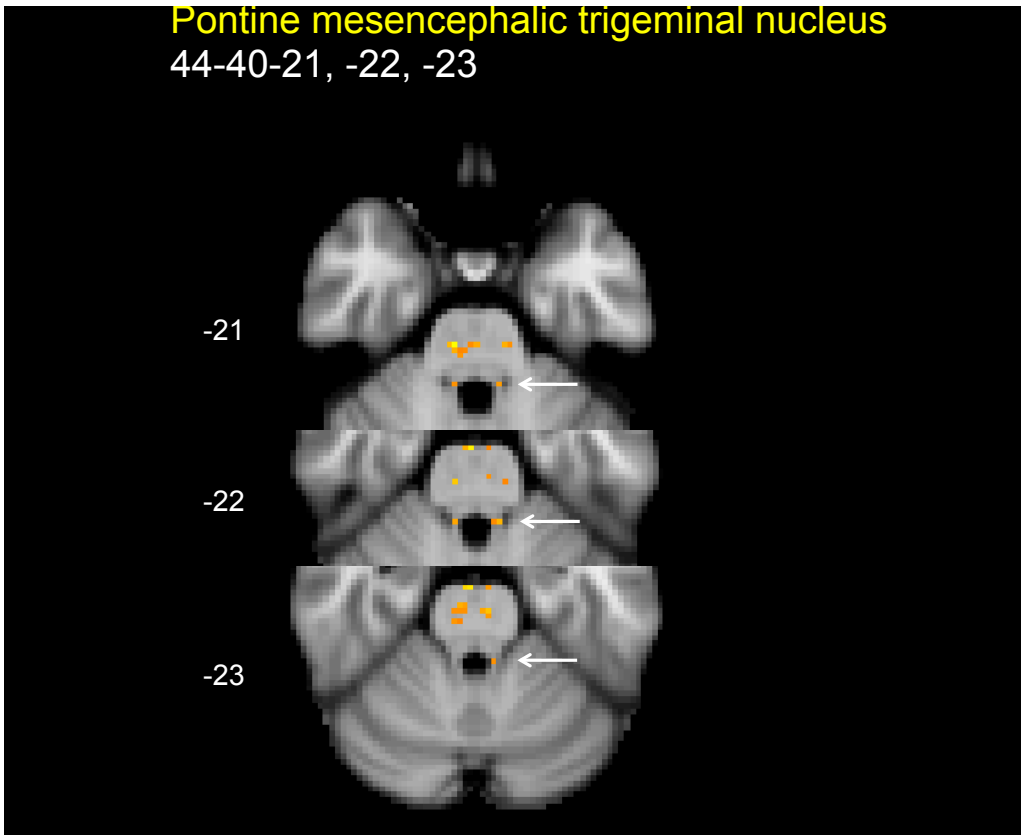


Figure 26. Pontine component of the Mesencephalic Trigeminal nucleus activated at orgasm compared to late stimulation. Combined group; Flame 1, Cluster 1.0, p <0.01.

2.2.3. Time-course analysis

In the combined partner and self group analysis of the time period spanning the last 10 sec of stimulation and the first 10 sec of orgasm (Figure 27), there was an overall pattern of increased activity leading up to orgasm, and a further change in activity following orgasm onset, with results similar to those seen in the differential contrasts presented in the previous section.

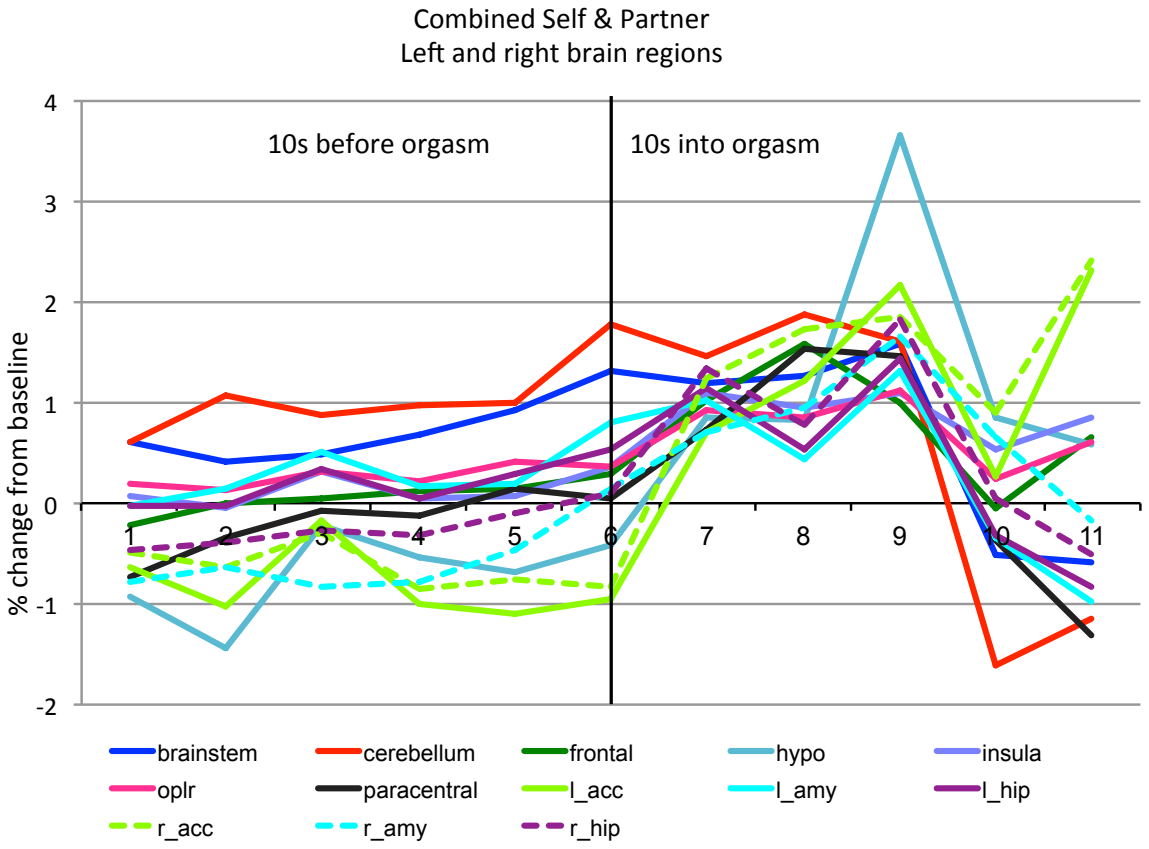


Figure 27. Combined self and partner group time course showed an overall pattern of increased activity leading up to orgasm.

2.2.4. Debriefing and descriptive data

During the post-scan debriefing session, all participants confirmed that they had experienced orgasm during the experiment, and had accurately indicated, by button press, the start of stimulation, onset of orgasm, end of orgasm, and end of recovery periods at the appropriate times. They also provided information about the physical and cognitive “cues” that they used to determine when the orgasm experience started, ended, and when they had recovered. They consistently underestimated the duration of their orgasm [please refer to Appendix F: Debriefing interview results).

The only significant difference between groups was that the partner-stimulation participants’ mean latency to orgasm was significantly longer than the self-stimulation participants’ mean latency to orgasm (476 versus 165 seconds): $t(8) = -2.67$, $p = 0.03$.

There were no significant differences between the self-stimulation-induced and partner-stimulation-induced groups in the mean duration of orgasm (23.5 versus 43.9 seconds) and mean duration of recovery (52 versus 50 seconds).

There were no significant differences in comparing the self and partner-stimulation-induced orgasm groups in age (46.8 versus 40.4); or mean subjective ratings (low =1 to high = 7) of arousal during stimulation (5.4 versus 5.6); orgasm intensity (5.1 versus 5.6); orgasm pleasure (4.8 versus 5.9); or orgasm satisfaction (5.0 versus 5.6).

For the self-stimulation-induced orgasm condition, the group mean motion displacements were: absolute = 1.48 mm, relative = 0.20. For the self-

stimulation-induced orgasm condition, the group mean motion displacements were: absolute= 1.10 mm, relative = 0.18.

A brief description of the behavioral data for the combined orgasm group follows [see Appendix F: Debriefing interview results). The mean age of the combined group was 43.6 years. The average head movement was 1.3 mm absolute, 0.2 relative. The participants had a mean latency to orgasm of 320 seconds. The average duration of orgasm was 33 seconds, while the period of recovery was 51 seconds. On a scale of 1 (low) to 7 (high) the participants rated orgasm intensity, orgasm pleasure, and orgasm satisfaction as 5.4, 5.4, and 5.3; respectively.

2.3. Discussion

As predicted, the results showed clear evidence that many brain regions were differentially activated during the course of genital stimulation leading up to and culminating in orgasm in these women. These activations include sensory, motor, reward, frontal cortical and brainstem regions, i.e., the genital sensory cortex (paracentral lobule), secondary somatosensory cortex (operculum SII, regions OP1 and OP4), precuneus, inferior parietal lobule, insula, hippocampus, amygdala, cerebellum, supplementary motor area, dorsal and ventral striatum (caudate, putamen, and nucleus accumbens), substantia nigra, the mesolimbic dopamine system (ventral tegmentum), hypothalamus, pons, anterior and posterior cingulate cortex, temporal pole, and the prefrontal cortex.

Furthermore, many of these brain regions also showed differential patterns of activity during the period of recovery, post-orgasm. These results are consistent with previous studies published by the Komisaruk lab (Komisaruk, Whipple et al, 2004; Komisaruk & Whipple, 2005; Komisaruk, Wise, et al, 2010, 2011; Wise et al., 2012); and are in direct contradiction to the findings of the Dutch group, who have reported reliable activations in only the cerebellum and pons at orgasm (Georgiadis et al., 2006; 2009; Huynh et al., 2013)

Also, in direct contradiction to Georgiadis et al. (2006; 2009) who report multiple regions of deactivation in temporal and prefrontal brain regions (right amygdala; right medial orbitofrontal; left lateral orbitofrontal; and left dorsolateral cortices), we found no evidence of activity below the global mean (baseline) compared to orgasm, for either frontal or temporal regions, as determined by the results of the ROI analyses conducted separately for the self-stimulation group, the partner-stimulation group, and the combined self-and-partner-stimulation group.

Furthermore, in the present study, not only did the frontal and temporal regions fail to “deactivate” (i.e., show activity below global baseline), but the activity of the prefrontal and temporal regions did not decrease relative to any of the peri-orgasm conditions. There were no significant contrasts involving activity greater just before orgasm than at orgasm (mid-stimulation > orgasm, late stimulation> orgasm), or activity after orgasm greater than during orgasm (early recovery > orgasm). These findings contradict the Dutch group’s claim that activity in the frontal and temporal cortical regions decreases at orgasm.

Contrary to what we considered might account for the discrepancy between our group and the Dutch group, we found no significant differences at orgasm (orgasm > late stimulation; orgasm > early recovery) between partner-stimulation and self-stimulation orgasm groups. This suggests that the major discrepancy between results of the Komisaruk lab and the Dutch group do not arise from the different type of stimulation used to induce orgasm (self versus partner), but perhaps from differences in imaging methods employed (fMRI versus PET), instructions to participants, and/or other elements of the research environment. It is important to note that one major limitation of the PET studies resides in the method's temporal resolution limitations compared to fMRI (Huettel, 2009). Georgiadis et al. (2009) acknowledge that the orgasm time period represented in their study included peri-orgasm events (sexual arousal and post-orgasmic satiety), introducing variability in their measurement such that the activity attributed to the orgasm scans should be considered "orgasm-related" rather than "orgasm-specific" (p. 3098). It is precisely the superior temporal resolution of fMRI that permits the analysis of the brain regional changes occurring during the transition from late stimulation ("going over") into orgasm, which is not feasible using PET.

The only significant differences between the self-stimulation and partner-stimulation groups were found during the stimulation period, the self-stimulation group showing more activity during mid-stimulation (than early stimulation), while the partner-stimulation group showed more activity during late stimulation (compared to mid-stimulation). It is possible that these differences stem from

group differences in latency to orgasm. The self-stimulation group, controlling their own stimulation, had significantly shorter latency to orgasm than the partner group. They may have “ramped up” sexual arousal earlier in the stimulation sequence than the partner-stimulation group, thereby showing more activity when mid-stimulation was compared to early stimulation.

Conversely, the partner stimulation group took longer to reach orgasm, and as a result, may have built up significantly more brain activation after what was a longer stimulation period for them. Thus, when late stimulation was compared to the mid-stimulation, they had experienced a significantly longer duration of stimulation. It is possible that this resulted in more cumulative brain activity than the self-stimulation group. Although the self-stimulation group did need to plan and execute their own stimulation, once the stimulation built-up to orgasm, it is possible that a final common “orgasm pathway” rendered the differences between self and partner stimulation less salient to the brain than the experience of the orgasm, itself.

A major limitation of the study is the small number of participants in each group (n = 5). It is conceivable that additional significant differences between groups might be observed with an increase in the number of participants per group. The small number of participants in each group may have also contributed to the lack of robust results for the group means for the contrast orgasm > late stimulation. And contrary to our prediction that we would find similar activity at orgasm (compared to mid-stimulation) in the genital sensory cortex, hippocampus, nucleus accumbens, and anterior cingulate cortex for both

groups, only the partner-stimulation group showed evidence of activations in these regions. Again, it may be possible that the lack of significant results for the self-stimulation group in this contrast stems from an interaction between the small number of participants and significantly shorter latency to orgasm (compared to the partner group). Future studies comparing self and partner-induced orgasm could address this issue. However, as group differences were found during stimulation but not orgasm, we conclude provisionally that there are no significant differences between self-stimulation-induced and partner-induced orgasms.

We found activations in the prefrontal regions at orgasm, rather than "deactivations" which the Dutch group interprets as a "disinhibition" that enables the "letting go" into orgasm. It should be noted that both activations and deactivations are relative to how the global baseline is calculated, and do not reflect an absolute measure. In regard to what underlying physiological processes might result in behavioral "disinhibition," it is conceivable that increased activity in a region, rather than decreased activity, could reflect a process of active inhibition contributing to behavioral disinhibition. In any case, as Georgiadis (2012) observed in a recent paper on the role of the cerebral cortex in human sexuality, " . . . the central control mechanisms of sexual activity are quite flexible . . . and that cortical brain regions play a critical part."

Our results, with evidence of activation rather than deactivation of the prefrontal cortex, are actually consistent with previous work done on reward and pleasure. We observed increased activity at orgasm in the medial orbitofrontal

region, an area identified as a “hedonic hot spot” (Berridge & Kringelback, 2008).

We made predictions based on results of our preliminary time-course study (Komisaruk, Wise, et al., 2010) that activity of some brain regions would increase gradually with early activation, others would build over the course of self –stimulation, others showing phasic activation just before orgasm, or at orgasm. These predictions were supported by the present results. Before comparing them, it is important to note the differences between our previous and current studies.

The previous study to which we refer used the beginning of orgasm as the group alignment point, and analyzed the 2 minutes before and 2 minutes after the onset of orgasm. ROIs were generated and mean time course activations were calculated from each ROI. The intensity of each ROI was calculated as a percent of its maximum over the course of its entire testing epoch, and the group averages plotted. We did conduct a similar type of time-course analysis examining the 10 seconds immediately before and after orgasm (discussed below).

As predicted, activity in the amygdala, hippocampus, and caudate was present during the early phases of stimulation (mid stimulation > early stimulation), increasing over the course of the sequence. We also found additional regions of activation at mid-stimulation in the prefrontal cortex, anterior cingulate cortex, hypothalamus, and the nucleus accumbens, which we predicted would show an increase later in the sequence.

The other regions we predicted would show an increase of activity as stimulation progressed were the genital sensory cortex (paracentral lobule), thalamus, and substantia nigra. We did, in fact, find evidence of increased activity of the paracentral lobule and thalamus as stimulation progressed (late stimulation > mid stimulation), and also in the secondary somatosensory cortex, insula, hippocampus, bilateral putamen, posterior cingulate, and the premotor and medial prefrontal cortices.

The regions that we predicted would show phasic activity at orgasm (cerebellum, anterior cingulate, inferior frontal gyrus) did show increased activity compared to mid-stimulation. We also found significant activations in additional sensory, motor, and reward regions, including the paracentral lobule, secondary somatosensory cortex, precuneus, insula, bilateral caudate, hippocampus, amygdala, nucleus accumbens, and ventral tegmentum.

The regions we predicted would be active at orgasm; i.e., the nucleus accumbens and the hypothalamus, were actually active throughout the sequence of stimulation, orgasm, and recovery.

With regard to the question of which processes are involved in the transition specifically from stimulation to orgasm, we report results for three different, but related, approaches. GLM analyses were conducted separately for the whole brain and brainstem. The results of the contrast, orgasm > late stimulation (the first 10 sec of orgasm > 10 sec immediately preceding orgasm) provides slightly different windows for examination of the transition into orgasm.

We also plotted the time-course of regions of interest for the “going over” period, which offers a dynamic overview, in 2-second increments (not constrained by the same statistical thresholding as the GLM analyses).

The results of the whole-brain analysis for orgasm > late stimulation, when more conservatively thresholded ($z = 1.65$, $p. < 0.05$), suggest that the transitioning into orgasm is essentially a major sensory-integration event, with increased activity of the genital sensory cortex, bilateral somatosensory cortex, left insula, precuneus, posterior cingulate, and inferior parietal lobule.

This same analysis, with the threshold reduced ($z = 1.5$, $p. < 0.01$) revealed increased activity in regions that were activated in other orgasm contrasts (orgasm> mid-stimulation and orgasm > early recovery). These regions include the right hippocampus, bilateral amygdala, right nucleus accumbens, septum, and anterior hypothalamus. There are two potential explanations of the failure to reach significance at the higher threshold: (1) the activity in these regions did not significantly “ramp up” immediately before orgasm, or (2) these regions would reach significance at the higher threshold with an increase in the number of participants. Further analyses adding more participants should provide clarification.

The structures of the brainstem are small, (some smaller than a voxel), so that using spatial smoothing (in combination with traditional cluster-forming thresholds) would likely preclude the ability to discern discrete activity in the brainstem.

The present brainstem analysis (cluster z = 1.0, p. < 0.01) provides insight into the neural bases of the autonomic, analgesic and reward components of orgasm. The present findings provide evidence of activation at orgasm of brain regions that stimulate sympathetic and parasympathetic activity, (i.e., posterior hypothalamus [Hess, 1957] and dorsal vagal nuclei [Monnier, 1968], respectively). There was also activation of lower brainstem regions implicated in pleasure, reward, and addiction (Berridge & Kringelbach, 2008), specifically, the ventral tegmentum (containing the cell bodies of the meso-corticolimbic dopamine system), and the substantia nigra. Our group reported previously that pain thresholds are elevated more than 100% during orgasm (Whipple & Komisaruk, 1985). In the present study, we observed significant activation of the periaqueductal gray (enkaphalin-releasing) and the dorsal raphe nucleus (serotonin-releasing), which are the major brainstem components that mediate endogenous analgesia (Basbaum & Fields, 1978).

From the vantage of the present time course study, which allowed for a dynamic overview of the activity in 2 sec increments occurring during the last 10 sec of stimulation through the first 10 sec of orgasm, we observed that activity in all ROIs increased at different rates during the period of late stimulation. Some regions had a high level of activity overall, including cerebellum, lower brainstem, secondary somatosensory cortex, and frontal cortex, with further increases at orgasm. Other regions, including the paracentral lobule, hippocampus, and insula had a steadily rising slope toward the onset of orgasm, with an increase at orgasm that continued throughout the 10 sec

orgasm period. Other regions, including the amygdala, had different patterns on the left and right sides with greater activity on the left during stimulation, and the right rising higher during the middle of the orgasm period.

The nucleus accumbens had peaks and valleys prior to the onset of orgasm. At orgasm onset, it had a steep ramp-up; another peak at about five sec into orgasm, a dip, and then the slope rose highest at the end of the 10 sec. As the mean orgasm duration was 33 seconds, it is possible that the accumbens activity had not yet reached its peak during the first ten sec of orgasm.

The hypothalamus also showed multiple peaks in activity, especially at orgasm, and continuing through a larger peak approximately 5 sec after orgasm onset. This is consistent with the results of the GLM analyses in which activation of the hypothalamus was observed during stimulation and orgasm, persisting into the recovery period.

Based upon the results of the various analyses of the transition from the later stimulation through orgasm, we conclude that “going over” into orgasm involves a complex interaction between sensory integration, motor, reward, and cognitive region, involving the autonomic nervous system. The evidence of activation of brain regions that control both sympathetic and parasympathetic activity at orgasm in this study of women suggests that, similar to the dual activation involved in orgasm in men (penile erection: parasympathetic function; ejaculation: sympathetic), both divisions of the autonomic nervous system contribute to the process of orgasm in women.

In addition to the small number of participants in the separate self- and partner-stimulation groups, another potential limitation of the study is that we combined both self-and partner-stimulation participants into one group for analysis. Although our findings of the self- and partner-stimulation groups yielded no significant group differences at orgasm, and served as a rationale for the combined orgasm group, further studies of self- and partner-induced orgasm are warranted.

Overall, our findings lead us to conclude that women's orgasm is a major neurological event, involving widespread activity in many regions of the brain Future effective connectivity studies should help elucidate how the activity of these regions develops and is integrated over the course of stimulation, orgasm, and recovery in the totality of the orgasm sequence.

3. Future Directions

The findings presented in this dissertation suggest that the brain is capable of responding robustly to both physical “touch” and mental “imagined” stimulation. As physical genital stimulation builds up and culminates in the major neurological event of orgasm, many brain regions implicated in sensory, motor, cognitive, and reward processes are recruited along the way. How these regions interact to create the complex phenomenological experiences of sexual arousal and orgasm are yet to be fully understood. Fortunately, we are at the brink of advances in methodology that will facilitate our ability to address this, and other questions, raised by this dissertation.

Recent work with real-time fMRI, in conjunction with compatible EEG/MEG, shows promise in allowing us to observe the brain at work (or play). Perhaps this method, in conjunction with effective connectivity data analysis techniques, will permit us to unravel the continuing mysteries of the orgasm sequence. How the various brain regions influence each other, activating and inhibiting one another, to produce the pleasures leading up to and including orgasm may well have applications beyond the bedroom.

This method has already been therapeutically applied as a tool for neurobiofeedback, with the goal to increase activity in the left amygdala (Zotev et al., 2014) and insula (Veit et al., 2012), which has been associated with enhanced mood regulation and reduced symptoms of anxiety and depression. It is possible that by studying people who are virtuosos in regulation of their pleasure systems, such as the easily orgasmic women in our study who activated

their genital sensory cortex simply by “imagining” genital stimulation, or the population of women who can literally “think” themselves into orgasm, previously studied by our group (Whipple et al, 1992), we will learn more effective strategies for helping mood-challenged individuals exercise the brain’s capacity for self-regulation.

References

Adrian, E. (1940). Double representation of the feet in the sensory cortex of the cat. *Journal of Physiology, 98*, 16.

Allison, T., McCarthy, G., Luby, M., Puce, A., & Spencer, D. D. (1996). Localization of functional regions of human mesial cortex by somatosensory evoked potential recording and by cortical stimulation. *Electroencephalography and Clinical Neurophysiology/Evoked Potentials Section, 100*(2), 126-140.

Aloni, R., & Katx, S. (1999). A review of the effect of traumatic brain injury on the human sexual response. *Brain Injury, 13*(4), 269-280.

Augustine, J. R. (1996). Circuitry and functional aspects of the insular lobe in primates including humans. *Brain Research Reviews, 22*, 229-244.

Aurbach, E., Heller, L., & Eagleman, D. (2009). Plasticity of somatosensory cortex after surgical body recontouring. Society for Neuroscience Abstracts, 39:363.25.

Baird, A. D., Wilson, S. J., Bladin, P. F., Saling, M. M., & Reutens, D. C. (2002). Hypersexuality after temporal lobe resection. *Epilepsy & Behavior, 3*(2), 173-181.

Basbaum, A. I., & Fields, H. L. (1978). Endogenous pain control mechanisms: Review and hypothesis. *Annals of Neurology, 4*(5), 451-462.

Berridge, K. C., & Kringelbach, M. L. (2008). Affective neuroscience of pleasure: Reward in humans and animals. *Psychopharmacology, 199*(3), 457-480.

Bridges, C. F., Critelli, J. W., & Loos, V. E. (1985). Hypnotic susceptibility, inhibitory control, and orgasmic consistency. *Archives of Sexual Behavior, 14*(4), 373-376.

Brodmann, K. (1909). Vergleichende lokalisationslehre der grobhirnrinde. *Barth, Leipzig.*

Brooks, J. C., Nurmikko, T. J., Bimson, W. E., Singh, K. D., & Roberts, N. (2002). FMRI of thermal pain: Effects of stimulus laterality and attention. *Neuroimage, 15*(2), 293-301.

Bufalari, I., Aprile, T., Avenanti, A., Di Russo, F., & Aglioti, S. M. (2007). Empathy for pain and touch in the human somatosensory cortex. *Cerebral Cortex, 17*(11), 2553-2561.

Chen, T. L., Babiloni, C., Ferretti, A., Perrucci, M. G., Romani, G. L., Rossini, P. M., Tartaro, A., & Del Gratta, C. (2008). Human secondary somatosensory cortex is involved in the processing of somatosensory rare stimuli: An fMRI study. *Neuroimage 40*(4), 1765.

Cox, R. W. (1996). AFNI: Software for analysis and visualization of functional magnetic resonance neuroimages. *Computers and Biomedical Research, 29*(3), 162-173.

Davidson, R. J. (1992). Anterior cerebral asymmetry and the nature of emotion. *Brain and Cognition, 20*(1), 125-151.

Del Gratta, C., Della Penna, S., Ferretti, A., Franciotti, R., Pizzella, V., Tartaro, A., Torquati, K., Bonomo, L., Romani, G.L. & Rossini, P. (2002). Topographic organization of the human primary and secondary somatosensory cortices: Comparison of fMRI and MEG findings. *Neuroimage, 17*(3), 1373-1383.

Derogatis, L. R. (1977). SCL-90–R: Administration, scoring and procedures manual I for the revised version of other instruments of the psychopathology rating scale series. *Baltimore: John Hopkins University.*

Di Noto, P. M., Newman, L., Wall, S., & Einstein, G. (2012). The hermunculus: What is known about the representation of the female body in the brain? *Cerebral Cortex,* doi:10.1093/cercor/bhs005.

Disbrow, E., Roberts, T., & Krubitzer, L. (2000). Somatotopic organization of cortical fields in the lateral sulcus of homo sapiens: Evidence for SII and PV. *The Journal of Comparative Neurology, 418*(1), 1-21.

Eickhoff, S. B., Lotze, M., Wietek, B., Amunts, K., Enck, P., & Zilles, K. (2006b). Segregation of visceral and somatosensory afferents: An fMRI and cytoarchitectonic mapping study. *Neuroimage, 31*(3), 1004-1014.

Eickhoff, S. B., Schleicher, A., Zilles, K., & Amunts, K. (2006a). The human parietal operculum. I. Cytoarchitectonic mapping of subdivisions. *Cerebral Cortex, 16*(2), 254-267.

Elliott, R., Dolan, R. J., & Frith, C. D. (2000). Dissociable functions in the medial and lateral orbitofrontal cortex: Evidence from human neuroimaging studies. *Cerebral Cortex, 10*(3), 308-317.

Farb, N. A., Segal, Z. V., Mayberg, H., Bean, J., McKeon, D., Fatima, Z., & Anderson, A. K. (2007). Attending to the present: Mindfulness meditation reveals distinct neural modes of self-reference. *Social Cognitive and Affective Neuroscience, 2*(4), 313-322.

Ferretti, A., Babiloni, C., Gratta, C. D., Caulo, M., Tartaro, A., Bonomo, L., Rossini, P.M. & Romani, G. L. (2003). Functional topography of the secondary somatosensory cortex for nonpainful and painful stimuli: An fMRI study. *Neuroimage, 20*(3), 1625.

Fisher, S. (1973). *The female orgasm: Psychology, physiology, fantasy.* Basic Books, New York.

Friedman, D. P., Murray, E. A., O'Neill, J. B., & Mishkin, M. (2004). Cortical connections of the somatosensory fields of the lateral sulcus of macaques: Evidence for a corticolimbic pathway for touch. *The Journal of Comparative Neurology, 252(3), 323-347.*

Georgiadis, J. R. (2012). Doing it… wild? on the role of the cerebral cortex in human sexual activity. *Socioaffective Neuroscience & Psychology, 2 Neurology, 252*(3), 323-347.

Georgiadis, J. R., Kortekaas, R., Kuipers, R., Nieuwenburg, A., Pruim, J., Reinders, A., & Holstege, G. (2006). Regional cerebral blood flow changes associated with clitorally induced orgasm in healthy women. *European Journal of Neuroscience, 24*(11), 3305-3316.

Georgiadis, J. R., Reinders, A., Paans, A. M., Renken, R., & Kortekaas, R. (2009). Men versus women on sexual brain function: Prominent differences during tactile genital stimulation, but not during orgasm. *Human Brain Mapping, 30*(10), 3089-3101.

Goligher, J. C., & Hughes, E. S. (1951). Sensibility of the rectum and colon. its role in the mechanism of anal continence. *Lancet, 1*(6654), 543-547.

Guldin, W., & Grüsser, O. (1998). Is there a vestibular cortex? *Trends in Neurosciences, 21*(6), 254-259.

Hämäläinen, H., Hiltunen, J., & Titievskaja, I. (2002). Activation of somatosensory cortical areas varies with attentional state: An fMRI study. *Behavioural Brain Research, 135*(1), 159-165.

Harlow, B. L., Wise, L. A., & Stewart, E. G. (2001). Prevalence and predictors of chronic lower genital tract discomfort. *American Journal of Obstetrics and Gynecology, 185*(3), 545-550.

Harris, R., Yulis, S., & Lacoste, D. (1980). Relationships among sexual arousability, imagery ability, and introversion-extraversion. *Journal of Sex Research, 16*(1), 72-86.

Hein, G., & Singer, T. (2008). I feel how you feel but not always: The empathic brain and its modulation. *Current Opinion in Neurobiology, 18*(2), 153-158.

Hess, W. R. (1957). *The functional organization of the diencephalon.* Grune & Stratton.

Hoechstetter, K., Rupp, A., Meinck, H., Weckesser, D., Bornfleth, H., Stippich, C., Berg, P., & Scherg, M. (2000). Magnetic source imaging of tactile input shows task-independent attention effects in SII. *Neuroreport, 11*(11), 2461-2465.

Huettel, S.A., Song, A.W., & McCarthy, G. (2009). Functional Magnetic Resonance Imaging-Second Edition. Sinaver Associates. Sunderland, MA.

Iwamura, Y., Tanaka, M., Sakamoto, M., & Hikosaka, O. (1993). Rostrocaudal gradients in the neuronal receptive field complexity in the finger region of the alert monkey's postcentral gyrus. *Experimental Brain Research, 92*(3), 360-368.

Jenkinson, M., Bannister, P., Brady, M., & Smith, S. (2002). Improved optimization for the robust and accurate linear registration and motion correction of brain images. *Neuroimage, 17*(2), 825-841.

Jenkinson, M., Pechaud, M., & Smith, S. (2005). BET2: MR-based estimation of brain, skull and scalp surfaces. In *Eleventh Annual Meeting of the Organization for Human Brain Mapping,* Vol 17. Toronto, Canada.

Jenkinson, M., & Smith, S. (2001). A global optimisation method for robust affine registration of brain images. *Medical Image Analysis, 5*(2), 143-156.

Jueptner, M., Ottinger, S., Fellows, S., Adamschewski, J., Flerich, L., Müller, S., .Weiller, C. (1997). The relevance of sensory input for the cerebellar control of movements. *Neuroimage, 5*(1), 41-48.

Kell, C. A., von Kriegstein, K., Rösler, A., Kleinschmidt, A., & Laufs, H. (2005). The sensory cortical representation of the human penis: Revisiting somatotopy in the male homunculus. *The Journal of Neuroscience, 25*(25), 5984-5987.

Kern, M. K., Jaradeh, S., Arndorfer, R. C., Jesmanowicz, A., Hyde, J., & Shaker, R. (2001). Gender differences in cortical representation of rectal distension in healthy humans. *American Journal of Physiology-Gastrointestinal and Liver Physiology, 281*(6), G1512-G1523.

Keysers, C., Wicker, B., Gazzola, V., Anton, J., Fogassi, L., & Gallese, V. (2004). A touching sight: SII/PV activation during the observation and experience of touch. *Neuron, 42*(2), 335-346.

Komisaruk, B. R., Beyer-Flores, C., & Whipple, B. (2006). The science of orgasm Johns Hopkins University Press.

Whipple, B., & Komisaruk, B. R. (1985). Elevation of pain threshold by vaginal stimulation in women. *Pain, 21*(4), 357-367.

Komisaruk, B. R., & Whipple, B. (1991). Physiological and perceptual correlates of orgasm produced by genital or non-genital stimulation. *The Proceedings of the First International Conference on Orgasm. VRP Publishers: Bombay, India,* 69-73.

Komisaruk, B. R., & Whipple, B. (2005). Functional MRI of the brain during orgasm in women. *Annual Review of Sex Research, 16*, 62.

Komisaruk, B. R., Whipple, B., Crawford, A., Grimes, S., Liu, W., Kalnin, A., & Mosier, K. (2004). Brain activation during vaginocervical self-stimulation and orgasm in women with complete spinal cord injury: FMRI evidence of mediation by the vagus nerves. *Brain Research, 1024*(1), 77-88.

Komisaruk, B.R., Wise, N., Frangos, E., & Allen, K. (2010). An fMRI time-course analysis of brain regions activated during self stimulation to orgasm in women. Society for Neuroscience Abstracts: 285.6.

Komisaruk, B. R., Wise, N., Frangos, E., Liu, W., Allen, K., & Brody, S. (2011). Women's clitoris, vagina, and cervix mapped on the sensory cortex: FMRI evidence. *The Journal of Sexual Medicine, 8*(10), 2822-2830.

Kross, E., Berman, M. G., Mischel, W., Smith, E. E., & Wager, T. D. (2011). Social rejection shares somatosensory representations with physical pain. *Proceedings of the National Academy of Sciences, 108*(15), 6270-6275.

Ladas, A. K., Whipple, B., & Perry, J. D. (1982). *The G spot and other recent discoveries about human sexuality* Holt, Rinehart, and Winston.

Ladas, A. K., Whipple, B., & Perry, J. D. (2005). *The G spot: And other discoveries about human sexuality.* Holt Paperbacks.

Leiblum, S. R., & Nathan, S. G. (2001). Persistent sexual arousal syndrome: A newly discovered pattern of female sexuality. *Journal of Sex &Marital Therapy, 27*(4), 365-380.

Loening-Baucke, V., Read, N., Yamada, T., & Barker, A. (1994). Evaluation of the motor and sensory components of the pudendal nerve. *Electroencephalography and Clinical Neurophysiology/Evoked Potentials Section, 93*(1), 35-41.

Mah, K., & Binik, Y. M. (2001). The nature of human orgasm: A critical review of major trends. *Clinical Psychology Review, 21*(6), 823-856. doi: 10.1016/S0272-7358(00)00069-6

Masters, W. H., & Johnson, V. E. (1970). Human sexual inadequacy. *Boston, 467*, 58.

Meana, M., Binik, Y. M., Khalife, S., & Cohen, D. (1997). Dyspareunia: Sexual dysfunction or pain syndrome? *The Journal of Nervous and Mental Disease, 185*(9), 561-569.

Meston, C., Levin, R., Sipski, M. L., Hull, E. M., & Heiman, J. (2004). Women's orgasm. *Annual Review of Sex Research, 15*, 173.

Michels, L., Mehnert, U., Boy, S., Schurch, B., & Kollias, S. (2010). The somatosensory representation of the human clitoris: An fMRI study. *Neuroimage, 49*(1), 177-184.

Monnier, M., Tissot, R., Fallert, M., & Schoneuberg, H. (1968). *Functions of the nervous system.* Elsevier Amsterdam.

Olivetti Belardinelli, M., Palmiero, M., Sestieri, C., Nardo, D., Di Matteo, R., Londei, A., . . . Romani, G. (2009). An fMRI investigation on image generation in different sensory modalities: The influence of vividness. *Acta Psychologica, 132*(2), 190-200.

Penfield, W., & Boldrey, E. (1937). Somatic motor and sensory representation in the cerebral cortex of man as studied by electrical stimulation. *Brain: A Journal of Neurology.*

Penfield, W., & Rasmussen, T. (1950). The cerebral cortex of man; a clinical study of localization of function. Macmillian.

Powell, T., & MOUNTCASTLE, V. B. (1959). Some aspects of the functional organization of the cortex of the postcentral gyrus of the monkey: A correlation of findings obtained in a single unit analysis with cytoarchitecture. *Bulletin of the Johns Hopkins Hospital, 105*, 133.

Pukall, C. F., Strigo, I. A., Binik, Y. M., Amsel, R., Khalifé, S., & Bushnell, M. C. (2005). Neural correlates of painful genital touch in women with vulvar vestibulitis syndrome. *Pain, 115*(1), 118-127.

Ramsey, J. D., Hanson, S. J., & Glymour, C. (2011). Multi-subject search correctly identifies causal connections and most causal directions in the DCM models of the smith et al. simulation study. *Neuroimage, 58*(3), 838-848.

Robinson, C., & Burton, H. (1980). Somatic submodality distribution within the second somatosensory (SII), 7b, retroinsular, postauditory, and granular insular cortical areas of M. fascicularis. *The Journal of Comparative Neurology, 192*(1), 93-108.

Rothemund, Y., Schaefer, M., Grüsser, S. M., & Flor, H. (2005). Localization of the human female breast in primary somatosensory cortex. *Experimental Brain Research, 164*(3), 357-364.

Ruben, J., Schwiemann, J., Deuchert, M., Meyer, R., Krause, T., Curio, G., Villringer, K., Kurth, R., & Villringer, A. (2001). Somatotopic organization of human secondary somatosensory cortex. *Cerebral Cortex, 11*(5), 463-473.

Smith, S. M., Jenkinson, M, Woolrich, M. W., Beckmann, C. F., Behrens, T., Johansen-Berg, H., Flitney, D. E. (2004). Advances in functional and structural MR image analysis and implementation as FSL. *Neuroimage, 23*, S208.

Swenson, Rand S. (2006). Review of Clinical Functional Neuroscience, Chapter 11: The Cerebral Cortex. Online version developed at Dartmouth Medical School. http://www.dartmouth.edu/~rswenson/NeuroSci/.

Tomarken A., & Keener, A. D. (1998). Frontal brain asymmetry and depression: A self-regulatory perspective. *Cognition & Emotion, 12*(3), 387-420.

Veit, R., Singh, V., Sitaram, R., Caria, A., Rauss, K., & Birbaumer, N. (2012). Using real-time fMRI to learn voluntary regulation of the anterior insula in the presence of threat-related stimuli. *Social Cognitive and Affective Neuroscience, 7*(6), 623-634. doi:10.1093/scan/nsr061 [doi]

Whipple, B., Ogden, G., & Komisaruk, B. R. (1992). Physiological correlates of imagery-induced orgasm in women. *Archives of Sexual Behavior, 21*(2), 121-133.

Wise, N., Frangos, E., & Komisaruk, B.R. (2010). Tactile imagery somatotopically activates genital sensory homunculus: fMRI evidence. Society for Neuroscience Abstracts: 800.6.

Woolrich, M.W., Ripley, B.D., Brady, J.M., & Smith, S.M. (2001) Temporal autocorrelation in univariate linear modeling of fMRI data. *Neuroimage,* 14(6), 1370-1386.

Yang, C., & Kromm, B. (2004). New techniques in female pudendal somatosensory evoked potential testing. *Somatosensory & Motor Research, 21*(1), 9-14.

Yoo, S. S., Freeman, D. K., McCarthy III, J. J., & Jolesz, F. A. (2003). Neural substrates of tactile imagery: A functional MRI study. *Neuroreport, 14*(4), 581.

Young, J. P., Herath, P., Eickhoff, S., Choi, J., Grefkes, C., Zilles, K., & Roland, P. E. (2004). Somatotopy and attentional modulation of the human parietal and opercular regions. *The Journal of Neuroscience, 24*(23), 5391-5399.

Zotev, V., Phillips, R., Yuan, H., Misaki, M., & Bodurka, J. (2014). Self-regulation of human brain activity using simultaneous real-time fMRI and EEG neurofeedback. *Neuroimage, 85*, 985-995.

Appendix A. Somatosensory cortical representation of female genitals, breast, and nipple

Genital representation in the primary somatosensory cortex (S1)

A major discrepancy in the literature regarding both male and female genitals is whether their primary somatosensory representation is located midline—in the mesial wall of the paracentral lobule—as depicted exclusively males by Penfield and Rasmussen (1950) —or more laterally, where the groin and trunk are represented on the homunculus. For the purpose of this proposal, only studies of women will be reviewed. Results vary depending on the methodology, the type of stimulation applied, the experimental design, and the population studied.

The three main methods of study of the somatosensory representation of the female genitals have been somatosensory evoked potentials (SSEP), functional Magnetic Resonance Imaging (fMRI), and Positron Emission Tomography (PET).

SSEP studies have largely supported the midline representation of the external female genitals. Allison et al. (1996), in a study of 18 epilepsy patients, found that stimulation of the dorsal pudendal nerve via electrodes placed on either side of the clitoris resulted in cortical activity in the mesial wall of the somatosensory cortex—the paracentral lobule—near the cingulate sulcus, anterior to the representation of the feet (in contrast to the Penfield map, which places the genitals posterior to the foot area). The authors concluded that

representation of the clitoris and perineum could be localized to the mesial paracentral lobule.

In another SSEP study, this time using 77 healthy participants, Yang and Kromm (2004) included stimulation of the dorsal nerve and the perineal nerves (other branches of the pelvic nerve which, in addition to the dorsal pudendal, innervate the clitoris and vagina). Stimulation of the dorsal nerve was accomplished via self-adhesive electrodes placed on both sides of the clitoris as well as on the clitoral hood. Stimulation of the perineal nerve was accomplished via insertion of a probe with two electrodes 1 cm into the vagina. Significant SSEPs from both perineal and dorsal nerve stimulation were detected from electrodes placed on the scalp near the mesial wall of the cortex, lending further support to the midline representation of the female external genitals and the vaginal introitus. The authors conclude that the somatosensory representation of the internal portion of the clitoris is yet to be determined, as the shallowness of the probe precluded deeper stimulation beyond 1 cm into the introitus.

The few neuroimaging studies done of the female genitals have yielded conflicting views as to their somatosensory representation. Functional magnetic resonance (fMRI) and positron emission tomography (PET) have both been used to investigate the representation of female genitals in the somatosensory cortex. Although there has been some recent support for Penfield's mesial paracentral representation, other studies have localized the clitoris more laterally on the dorsal surface of S1—in the homuncular region of the groin and trunk.

Georgiadis et al. (2006) used PET to study the brain correlates of clitoral

stimulation (done by the participant's partner) and orgasm in 12 healthy women. Clitoral stimulation was reported to result in bilateral activation of the dorsal surface of the postcentral gyrus in S1 and unilaterally in the left S2 in the parietal operculum, with the strongest overall activation in S2.

Additional support for a more lateral somatosensory representation of the female clitoris comes from an fMRI study of 15 healthy women done by Michels et al. (2010). Bilateral dorsal clitoral nerve stimulation via self-attaching electrodes was applied using participant-specific calibrations to adjust stimulation such that it was neither painful nor arousing. A boxcar design was used, alternating short periods of stimulation (12 s) with rest (18 s) to intentionally avoid creating sexual arousal. Lateral, but not mesial, primary (S1) somatosensory activations were reported, as well as secondary somatosensory (S2) activation in the parietal operculum. The supplementary motor area (SMA) was also activated, presumably due to indirect influence of clitoral stimulation on reflex pathways on the external sphincter muscle tone. Hemispheric differences were noted, with stronger left-sided somatosensory cortex activations. Additionally, the left insula was activated, which the authors speculate as being related to the insula's role in viscerosensory processing.

Support for the midline paracentral somatosensory representation of female genitals comes from a recent study conducted by Komisaruk, Wise, et al., (2011). As cited by Di Noto et al., (2012) our fMRI investigation of 11 healthy women is the first to systematically map the clitoris, vagina, cervix, and nipple on the sensory cortex. The participants self-stimulated the clitoris, anterior wall of

the vagina, cervix, and nipple in separate boxcar trials, 30 s rest followed by 30 s stimulation repeated 5 times in succession (Komisaruk, Wise, et al., 2011). Participants rhythmically tapped the clitoris for the clitoral self-stimulation trials. An S-shaped acrylic cylinder was used by participants for self-stimulating the anterior wall of the vagina, while a straight acrylic cylinder with a rounded tip was used for cervical self-stimulation trials. Nipple stimulation was accomplished by using the right hand to tap the left nipple rhythmically. Participants were instructed to self-stimulate to “comfortable” intensity, but not directed to either seek or avoid sexual arousal during stimulation (Komisaruk, Wise et al., 2011, p. 2824).

Results of the mapping study indicate that the responses to clitoral, vaginal, and cervical self-stimulation were clustered in the mesial paracentral lobule, with differentiable but overlapping activations. Consistent with the original Penfield and Rasmussen male homunculus, the female genitals were represented deep within the cortex, with activations for the clitoris located superior to that of the cervix and vagina. Also noted were additional activations in the dorsolateral region of the paracentral cortex, corresponding to the groin region for all of the genital stimulation conditions. In addition, stimulation of the nipple unexpectedly activated the mesial paracentral lobule as well as the more lateral chest/trunk region (Komisaruk, Wise, et al., 2011). (See appendix Figure 2.)

A possible explanation for the discrepancy in neuroimaging results

There are a number of possible explanations for the discrepancy between the studies that support the more lateral somatosensory representation of the female genitals (Georgiadis et al., 2006; Michels et al., 2010), and the Komisaruk et al. (2011) study supporting the Penfield/Rasmussen mesial paracentral representation of the female genitals. Of note is that the Georgiadis et al. (2006) study used PET—a method whose spatial resolution tends to be more diffuse and less specific than that of fMRI (Huettel et al., 2009).

Also to be considered is that the Michels et al. (2010) study, although employing the more spatially specific fMRI, used short intervals of electrical stimulation intentionally designed to avoid arousal rather than manual mechanical stimulation of the clitoris as in the Komisaruk et al. (2011) mapping study. It is possible, given the stimulus parameters of the Michels et al. (2010) study, that the stimulation delivered was sufficient only in significantly activating the adjacent skin of the groin region—and not the genital sensory cortex per se.

Somatosensory representation of the breast and nipple

There have not been many studies of the cortical representations of the trunk and nipple in humans since Penfield & Rasmussen (1950) postulated that the breast, like the labia and buttocks, were represented in the mesial paracentral lobule.

Rothermund et al. (2005) conducted an SSEP study that localized the representation of the nipple between the groin and the first digit, 15 mm lateral to

the longitudinal fissure of the contralateral hemisphere. An fMRI study of the breast (Aurbach, 2009) also localized the cortical representation of the breast lateral to the longitudinal fissure. And as already discussed, in addition to activation in the more lateral region of S1 corresponding to the trunk, support for the midline paracentral lobule somatosensory representation of the nipple comes from a recent study by Komisaruk, Wise et al. (2011)

Appendix B. Interview Questions

Amendment Request to project title: FMRI Analysis of Orgasm in Women
P.I. Name: Nan Wise, PhD Cand.
Protocol #: 12-71M

Note: For all interviews: participants will be informed at the outset that they are not required to answer any question about which they feel uncomfortable.

Pre Scan Interview

Questions about study participation:

How did you learn about the study?
What motivated you to participate in the study?
Do you have concerns about being in the fMRI scanner with the objective to experience pleasure or have an orgasm?
Do you other fears/reservations about participating?
Have you ever been in a sexuality study before?
Did you tell anyone about your upcoming participation in this study?
Whom, how many, and under what circumstances?

P**hysical and sexual history questions:**

How/when/from whom do you learn about sex?
How do you feel about your body?
At what age did you start to menstruate?
If premenopausal, when was your last menstrual period?
How did you experience your transition to adolescence?
How did others experience your transition to adolescence?
Have you ever been pregnant?
Given birth? What was your experience with labor and childbirth?
Do you use birth control? If so, which type?
Are you on any medications? If so, which?
Are you post-menopausal?
Taking hormone replacement therapy?
Have you ever had an upsetting childhood experience having to do with sex?
Any troubling sexual experience in adulthood?

Influences: Family

Did your parents allow you to discuss or ask questions about sexual topics?
Did your parents openly show affection toward each other?
Were your parents physically affectionate toward you?

What was the attitude in your home about nudity?
How do you think your parents viewed sexuality?
What was their attitude toward your developing sexuality?
Did your family's religious beliefs affect your feelings toward sex?
Did you talk about sex with your siblings?
As a child, did you play games that had sexual content?
How do you think your siblings feel/felt about their sexuality?

Dating history:

Can you describe your first dating experience?
How did your parents react to your starting to date?
Can you describe your dating history?
Please describe your first sexual experiences: kissing, petting, intercourse.
Can you describe your significant romantic relationships to date?

Current Relationship:

Are you currently in an intimate relationship? Please describe.
Monogamous or other?
How happy are you with the relationship/s? With your sex life?

General questions:

Do you consider yourself heterosexual, homosexual, bisexual, other?
Has your sexual orientation or attraction changed over time?
Do you think you have more interest in sex than the average woman?
Do you think you are more comfortable with sexuality than the average woman?
Have you always been comfortable with your sexuality? If not, please elaborate.
Do you masturbate at home? Method? Frequency? Fantasies?
Do you regularly use a vibrator? Dildo? Sex toys? With partner or alone?
Preference for type of stimulation during sexual activity? Clitoral, vaginal, cervical?
Preferred type of sexual activity (giving/getting, vaginal, oral, anal)?
During which kind(s) of stimulation are you (most) satisfied/orgasmic?
Do you have multiple orgasms? If so, how regularly and under what circumstances?
Have you ever had difficulty experiencing orgasm?
Do you typically prefer self- or partner-stimulation?
What are your sexual turn-ons?
Do you enjoy pornography? If so, which type(s)?
Do you enjoy being exhibitionistic? Voyeuristic? BDSM? Other?
Have you engaged in having sex in front of other people (aside from your partner)?
Have you had group sex?
Can you "think " yourself into orgasm without any physical stimulation?
Do you believe there is something unique about your sexuality?

If you could share your most important lessons in becoming comfortable with your sexuality, what would they be?
Do you exercise regularly
Have you gone to sexuality workshops? Studied Tantra?
Do you practice yoga?

Post Scan Interview

Debriefing questions

How are you feeling after the study? Is there anything you wish to discuss or share?
Was the overall experience similar to your expectations? Different? Better? Worse?
What was the most challenging part of the scanner study for you?
Overall, how affected were you by the scanner environment?

On a scale of 1-7 where 1 is "not important" to 7 which is "very important" -- how important were each of the following to your experience of orgasm in the scanner?

- having to keep still
- embarrassment
- vocalization
- breath holding
- scanner noise
- [subject allowed to add items]

How did the constraint on your movement affect your experience?
How were you affected by keeping track of your experience—i.e., button presses to indicate start stimulation, start orgasm, end orgasm, end recovery?
Would you participate in this study again if you had the chance?
Can you recommend any way to improve the study procedures or experience?

Operationally defining conditions for timing purposes

a. How would you describe the feeling you have just before having an orgasm?
1b. How would you describe the feeling during an orgasm?
1c. How would you describe the feeling following an orgasm?

How did you know your orgasm was beginning?
How did you decide when to press the button (orgasm approaching, orgasm starting, etc.?).
What cues inform you that your orgasm is starting (please be specific—bodily sensations, changes in breathing, muscular contractions, racing heart, etc.)

How did you know your orgasm ended? Did you press the button once the orgasm was completely over or did you sense it was about to end (please be specific—bodily sensations, changes in breathing, muscular contractions, etc.).
How did you gauge when you were fully recovered from your orgasm?

Assessment of degree of arousal during imagery stimulation trials:

How vividly were you able to imagine clitoris stimulation?
Scale from 1 (no image/sensation) to 7 (very vivid image/sensation)
Were you sexually aroused during the clitoris imagery condition?
If so, how aroused on a scale of 1 (low) to 7 (high)?
How vividly were you able to imagine nipple stimulation?
Scale from 1 (no image/sensation) to 7 (very vivid image/sensation)
Were you sexually aroused during the nipple imagery condition?
If so, how aroused on a scale of 1 (low) to 7 (high)?
How vividly were you able to imagine dildo stimulation?
Scale from 1 (no image/sensation) to 7 (very vivid image/sensation)
Were you sexually aroused during the imagine dildo condition?
If so, how aroused on a scale of 1 (low) to 7 (high)?
How vividly were you able to imagine speculum stimulation?
Scale from 1 (no image/sensation) to 7 (very vivid image/sensation)
Were you sexually aroused during the imagine speculum imagery condition?
If so, how aroused on a scale of 1 (low) to 7 (high)?
Did you find any of the imagery conditions unpleasant or aversive?
If so, which condition?
How unpleasant/aversive on a scale of 1 (low) to 7 (high)?

Assessment of degree of arousal during physical stimulation trials:

Were you sexually aroused during the clitoris self-stimulation condition?
If so, how aroused on a scale of 1 (low) to 7 (high)?
Were you sexually aroused during the nipple self-stimulation condition?
If so, how aroused on a scale of 1 (low) to 7 (high)?

Assessment of self-induced orgasm condition:

How aroused were you during self-stimulation on a scale of 1 (low) to 7 (high)?
Were you fantasizing during self-stimulation? If so, content?
Did you fantasize during orgasm? If so, content?
How intense was your orgasm on a scale of 1 (low) to 7 (high)?
How pleasurable was your orgasm on a scale of 1 (low) to 7 (high)?
How satisfying was your orgasm on a scale of 1 (low) to 7 (high)?
Did you ejaculate during your orgasm?
Did you experience genital contractions?
If so, how many and how strong?
Did you hold your breath at orgasm?
Did your breathing change during stimulation?
Did you vocalize or make noise during your orgasm?

Did you have trouble staying still?
How much do you think you moved during orgasm on a scale of 1 (very little movement) to 7 (high movement)?
Please estimate the duration of your orgasm (in seconds).

Assessment of partner-induced orgasm condition:

How aroused were you during stimulation by your partner: scale of 1 (low) to 7 (high)?
Were you fantasizing during stimulation by your partner? If so, content?
Did you fantasize during orgasm? If so, content?
How intense was your orgasm on a scale of 1 (low) to 7 (high)?
How pleasurable was your orgasm on a scale of 1 (low) to 7 (high)?
How satisfying was your orgasm on a scale of 1 (low) to 7 (high)?
Did you ejaculate during your orgasm?
Did you experience genital contractions?
    If so, how many and how strong?
Did you hold your breath at orgasm?
Did your breathing change during stimulation?
Did you vocalize or make noise during your orgasm?
Did you have trouble staying still?
How much do you think you moved during orgasm: scale of 1 (very little movement) to 7 (high movement)?
Please estimate the duration of your orgasm (in seconds).

Assessment of difference between self-stimulation-induced orgasm and orgasm induced by partner stimulation:

How would you compare your orgasm induced by self-stimulation with that induced by your partner during the experiment?
    Intensity? Quality? Satisfaction?
How did these experiences differ from orgasm experiences outside the scanner? Please elaborate.

Appendix C. The secondary somatosensory cortex (S2)

The secondary somatosensory cortex, like its counterpart S1, is located adjacent to a major brain sulcus, occupying the upper bank of the lateral sulcus in the parietal operculum. First identified by Adrian (1940), who showed that cats' paws were represented not only in S1, but also in an adjacent region, much less is known about S2, particularly in humans.

Region S2 in primates and humans, which refers to the totality of S2, has customarily been divided into three anatomical areas, with the area adjacent to S1 at the lateral sulcus known as the parietal ventral area (PV). Adjacent and posterior to area PV is area S2 (not to be confused with region S2). Lastly, the ventral somatosensory area (VS) lies deeper in the sulcus, with its inner edge bordered by the insula and the outer edge adjoining the PV.

Using ten post-mortem brains, Eickhoff et al. (2006a) further delineated the cytoarchitecture of S2, (see Figure 1b), identifying four distinct, bilateral, architectural areas of the human parietal operculum as follows: OP 1, roughly equivalent to area S2; OP 3, corresponding to area VS; and OP 4, which is analogous to area PV. Of these regions, only OP 2 does not appear to have an S2 homologue in the infahuman primate brain, although researchers examining the cortex posterior to the infrahuman primate S2 have described the region as responding to input from the auditory and vestibular systems (Robinson & Burton, 1980; Guldin & Grusser, 1998).

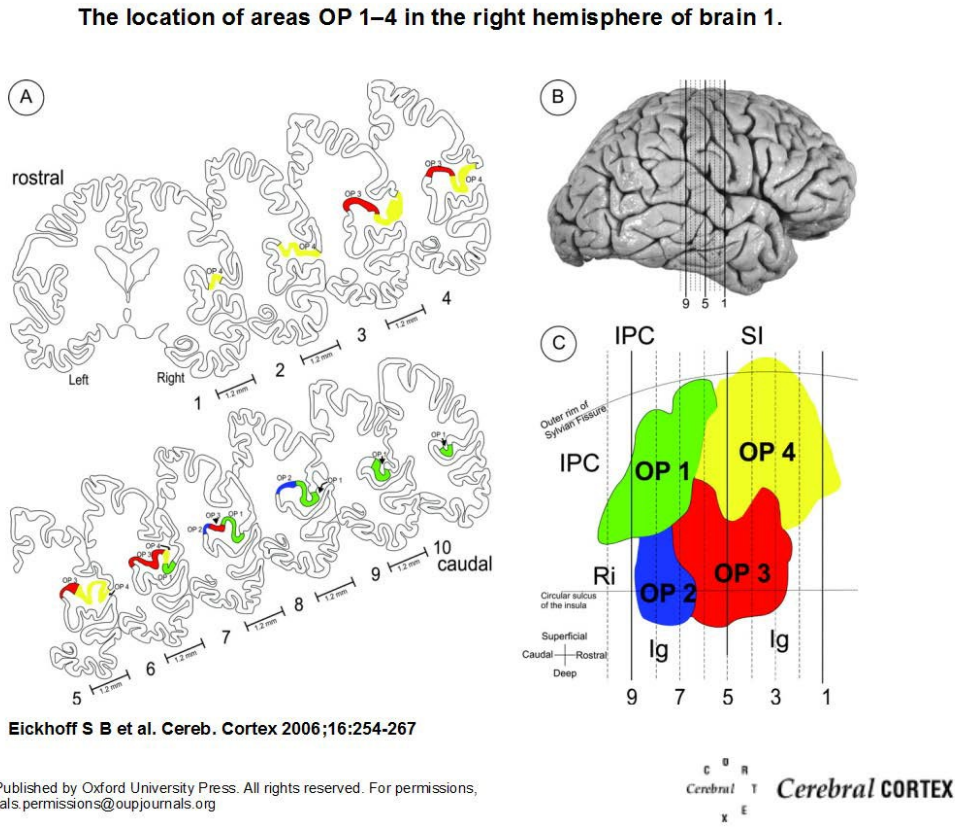


Figure 1b.The location of areas OP 1–4 in the right hemisphere of brain 1. (A) Drawings of serial coronal sections (right hemisphere displayed on the right side) with OP 1–4 marked by different colors. The section numbers 1–10 correspond to the numbers in (C), where the planes of sectioning are marked by lines. (B) Brain 1 from right lateral. (C) Flat map of OP 1–4 (same brain). Reprinted from The Human Parietal Operculum. I. Cytoarchitectonic Mapping of Subdivisions, S. B. Eickhoff et al, 2006. *Cerebral Cortex,* 16, Vol. 2 254-267 2006 Oxford University Press.

S2 connectivity

Region S2 receives connections from S1, and also from non-specific thalamic nuclei (Swenson, 2006). The left and right S2 areas of region S2 are densely interconnected such that stimulation of one side of the body will bilaterally activate area S2. Area S2 is also connected with BA 1 and 3b, and projects to area PV, BA 7b (part of the somatosensory association area), the

insular cortex, amygdala, and hippocampus. Area PV of region S2 connects with BA 5 and the premotor cortex (Augustine, 1996).

In summary, region S2 is anatomically connected to play a key role in relaying somatic information from S1 and S2 to limbic structures by way of the insula, thereby creating a potential cortico-limbic pathway for touch (Friedman et al., 2004).

Overview of functions of S2

In contrast with S1, S2 is believed to perform functions such as arousal- produced modulation of sensory activity. S2 also appears to participate in aspects of somatosensory attention, learning, and memory (Chen et al., 2008). There is considerable evidence that S2 plays a large role in selective somatosensory perception, and that in contrast to S1, S2 is specifically active as a function of modulation of attention to somatosensory input (Hoechstetter et al., 2000; Broocks et al., 2002; Hamalainen et al., 2002).

In humans, there is evidence for the existence of complete, somatotopically organized body maps in areas OP 4 and S2 of region S2, most likely analogous to infrahuman primate areas S2 and PV. The lip, face, hand, trunk, and foot are represented in a lateral to medial sequence, respectively (Del Gratta et al., 2000). Other areas of region S2 do not appear to have such clear organization (Disbrow et al., 2000). It is thought that the somatic maps of region S2, such as those responding to somatosensory stimulation of the hand, possess relatively large receptive fields that non-

differentially encompass many or even all of the fingers, in contrast with the digit-by-digit resolution of the S1 map of the fingers and hand (Ruben et al., 2001).

That many different functions have been ascribed to S2 has led to some confusion about its role. Perhaps the four distinct cytoarchitectural areas of S2 modulate different somatosensory processes. Further research correlating results of functional imaging data with specific cytoarchitectural areas for clarification is indicated (Eickhoff et al., 2006a).

S2 and pain

In S2, non-painful stimuli activate distinct foci compared to painful stimuli, which produce more posterior, diffuse activation (Ferretti et al., 2003). Pukall et al. (2005) conducted an fMRI study comparing control participants with women suffering from vulvar vestibulitis syndrome (VVS), which is the most common cause of dyspareunia in pre-menopausal women (Meana et al., 1997), affecting up to 12% of the population (Harlow et al., 2001). Painful pressure applied to the posterior portion of the vulvar vestibule resulted in bilateral activation in S2 (but, curiously, no activity in S1), with significantly greater activity in S2 on the left side. Women suffering from VVS showed more significant activations of S2 and reported higher pain intensity ratings to comparable pressure than did control participants, leading the authors to suggest that VVS involves an augmented sensory response to stimulation, similar to processes that may underlie other disorders such as fibromyalgia

and irritable bowel syndrome (Pukall et al., 2005).

S2 has also been implicated in the social pain of rejection. Kross et al., (2011) used fMRI to demonstrate that participants who have recently experienced the painful dissolution of a romantic relationship showed similar activations in S2 and dorsolateral insula when viewing a head shot of their former partner as when subjected to physical pain during the study. The authors conclude that physical pain and emotional suffering are not only both distressing, but appear to share common somatosensory representation.

There is also some support for the involvement of S2 in empathy (Hein & Singer, 2008), both in response to another's physical pain (Bufalari et al., 2007) and similar S2 activations occurring while observing someone being touched (Keysers et al., 2004).

S2 and the interpretation of sensation

Penfield and Rasmussen (1950) reported that when electric stimulation was applied in the central fissure, patients rarely described sensation in the "lower sacral and genital regions," which the authors attributed to a "false sense of modesty" (p. 418). When sensation was indeed reported in the penis, it was not described as erotic. It is possible that, in addition to the social inhibitions referred to by Penfield and Rasmussen, the type of stimulation, and the context in which it was delivered, contributed to the lack of erotic genital sensation reported.

It is not clear how electrical stimulation of the surface of the brain would

differentially affect neurons responsive to stimulation of deep receptors (S1 areas 3a and 2), versus those predominantly responsive to stimulation of cutaneous receptors (S1 areas 3b and 1). It is also doubtful that electrical stimulation of the surface of the brain would effectively penetrate to the level of region S2 and the insula (Di Noto et al., 2012), which may have limited the type of sensation experienced to that of a more prosaic, than erotic, nature. In addition, the anxiety-inducing context of the stimulation—which occurred in a surgical suite with the patient's brain exposed—may have interacted with the above factors to reduce the probability that the stimulation would be experienced erotically. Context, alone, could significantly impact whether genital stimulation is experienced as erotic. Women routinely experience the vaginal penetration by a speculum during a gynecologic exam as non-erotic, although a comparable experience of vaginal penetration under a completely different set of circumstances could be deemed both pleasurable and erotic.

There is some evidence that region S2 may play a role in the interpretation of sensation as erotic. This will be presented in the following section.

S2 and the insula as accessory areas to S1

A PET orgasm study that supports the notion that erotic sensation may be encoded in places other than S1 reported that the strongest activation observed during the clitoral stimulation condition (described by participants as erotically pleasurable) occurred in left S2. This finding, in combination with

other studies linking S2 to somatosensory attention, led the authors to speculate that S2 may be involved in the appraisal of tactile genital stimulation as sexual (Georgiadis et al., 2006). Additionally, the insula, with its rich connections with much of the cerebral cortex including sensory association areas and S2, has been identified as playing a role in visceral sensory processing in a number of recent studies (Kern et al., 2001; Komisaruk et al., 2004; Komisaruk & Whipple, 2005; Komisaruk et al., 2011; Eickhoff et al., 2006b).

S2 representation of the anus and rectum

As the anal canal is innervated by somatosensory afferents from the pudendal nerve (Golinger & Hughes, 1951), while the is rectum innervated by visceral pelvic nerve afferents (Loening-Baucke et al., 1994) it is of interest that anal sensations were processed in OP 4, human area PV, the same cytoarchitectural area where hands (Eickhoff et al., 2006a), feet (Young et al., 2004), and the penis (Kell et al., 2005) are represented, while rectal stimulation evoked activations more anteriorly, on the precentral operculum between OP 4 and BA 44 –not within region S2 (Eickhoff et al., 2006b), indicating that somatosensory and visceral afferents may have functionally and anatomically distinct representations.

Appendix D. Additional Imagery study results

Preliminary analysis results

Differential contrasts

CTS>CTM (clitoris touch stimulate > clitoris touch model)
CIS>CIM (clitoris imagine stimulate>clitoris imagine model)

Apparent in Figures 1 and 2, less overall activity is evident in the differential contrast, CTS>CTM (Figure 1), than in in the contrast CIS>CIM (Figure 2) when both contrasts are seen at the cluster threshold z= 1.65, p< 0.05.

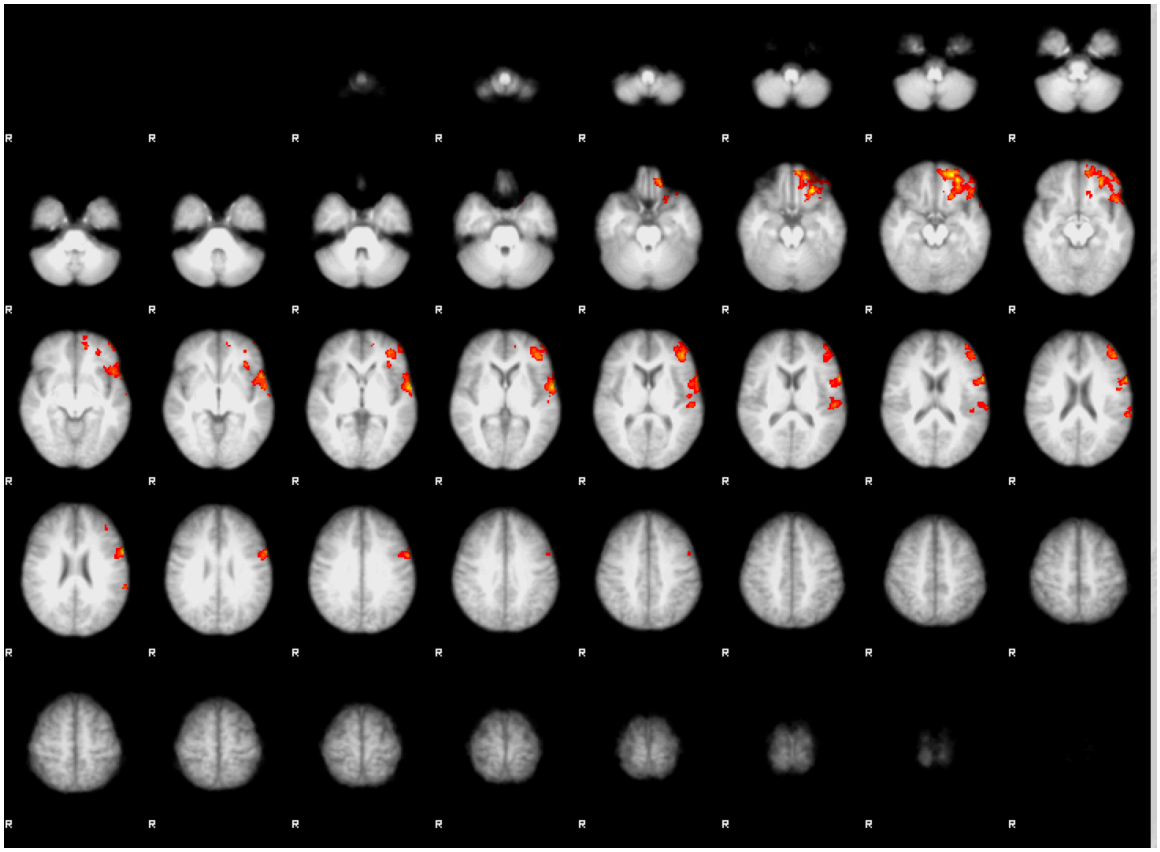


Figure 1. Clitoris touch stimulate>clitoris touch model; Flame 1, Cluster 1.65, p<0.05.

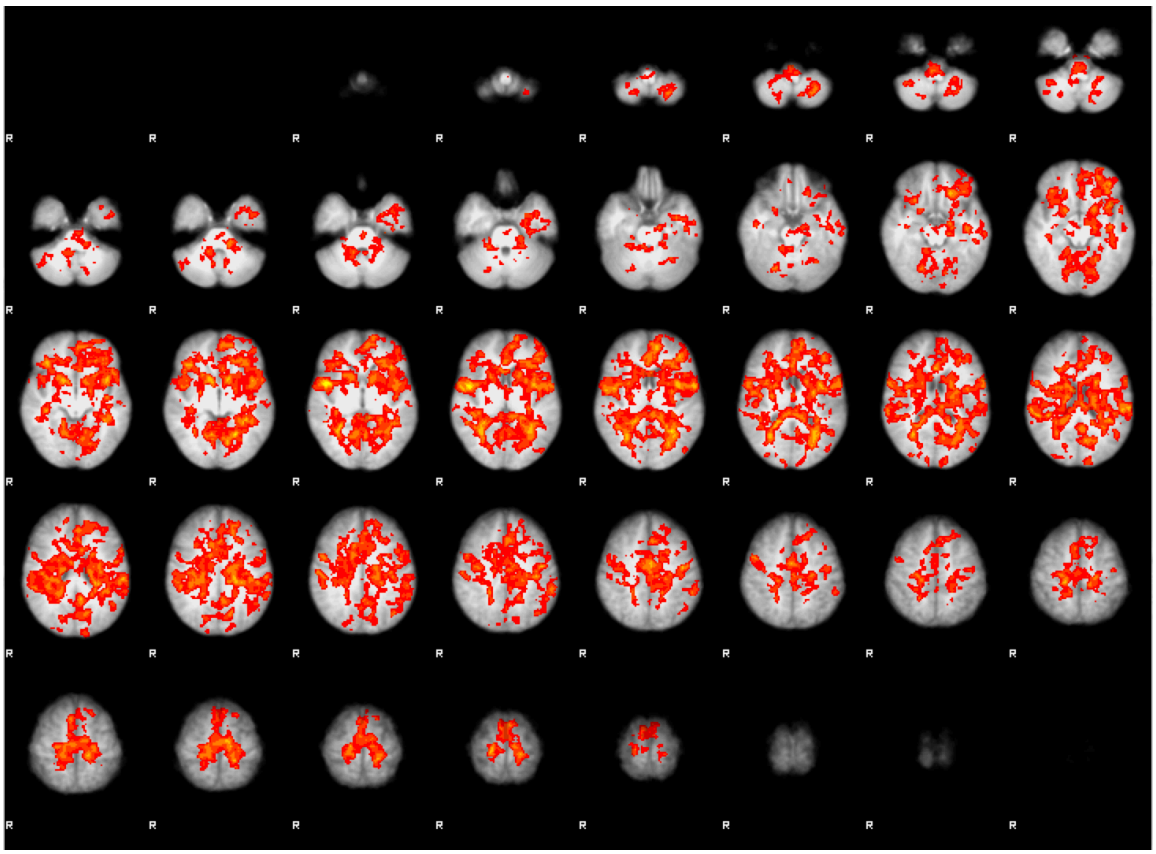


Figure 2. Clitoris imagine stimulate>clitoris imagine model; Flame 1, Cluster 1.65, $p<0.05$.

This observation led to an examination of the results of the basic contrasts above and below the global mean (baseline) for the constituent contrasts, i.e., CTS, CTM, CIS, and CIM which indicated that the disparity of the results of the differential contrasts seen in Figures 1 and 2 was caused by activity below the global baseline in the constituent contrasts. This finding indicated that the results of the differential contrasts should be contrast-masked, post-threshold, with the corresponding basic contrasts (voxels above baseline) to assure that the results viewed would be driven by positive changes in the BOLD signal. Similar results were found for the differential contrasts for the Nipple Touch Stimulate> Nipple Touch Model and Nipple Imagine Stimulate> Nipple Imagine Model comparisons.

Final analysis results

Physical and imagined stimulation of the clitoris and nipple (pre-threshold masked with imagery regions of interest; contrast-masked post-threshold)

Paracentral lobule activation: Physical stimulation conditions

CTS>CTM (clitoris touch stimulate > clitoris touch model)
NTS>NTM (nipple touch stimulate>nipple touch model)

The paracentral lobule was activated for both physical stimulation conditions, with more apparent activation evident in the clitoris stimulation condition, (Figure 3), than in the nipple stimulation condition (Figure 4).

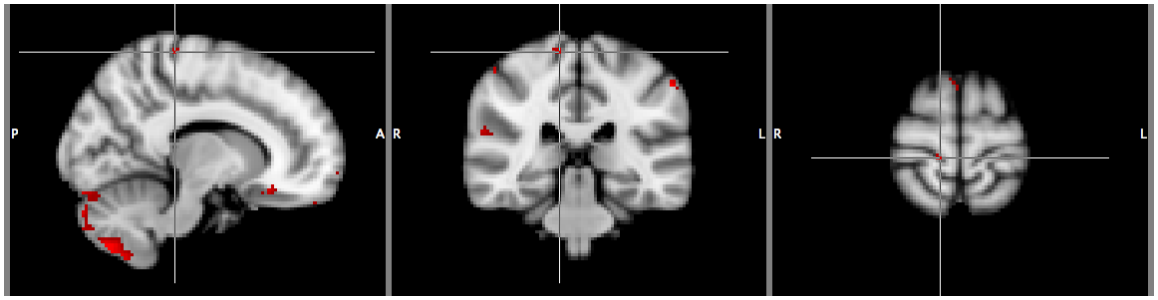


Figure 3. CTS > CTM, Flame 1, z=1.0, p <0.01; Paracentral lobule.

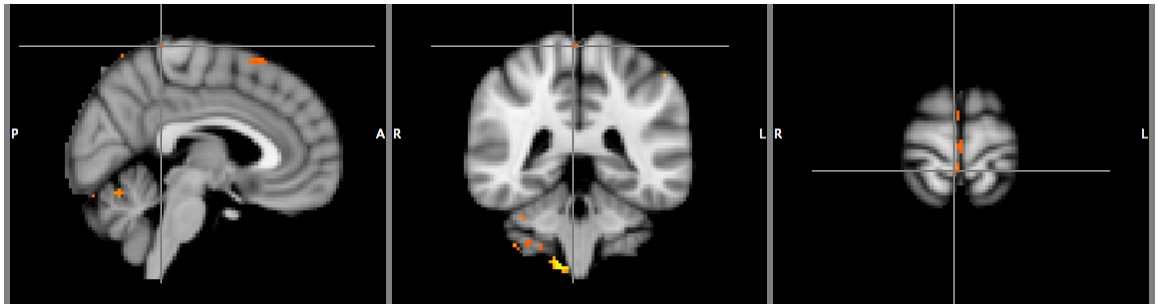


Figure 4. NTS > NTM, Flame 1, z=1.0. p <0.01; Paracentral lobule.

Paracentral lobule activation: Imagined stimulation conditions

CIS>CIM (clitoris imagine stimulate > clitoris imagine model)
NIS>NIM (nipple imagine simulate > nipple imagine model)
CIS>NIS (clitoris imagine stimulate> nipple imagine stimulate)

Bilateral activation of the paracentral lobule is noted in the clitoris imagine stimulation condition (Figure 5), with a similar pattern, to a lesser degree, observed in the nipple imagined stimulation contrast (Figure 6), as evidenced by the result of the contrast CIS>NIS (Figure 7).

There were no significant differences observed in the paracentral lobule when the physical conditions were statistically compared to the imagery conditions.

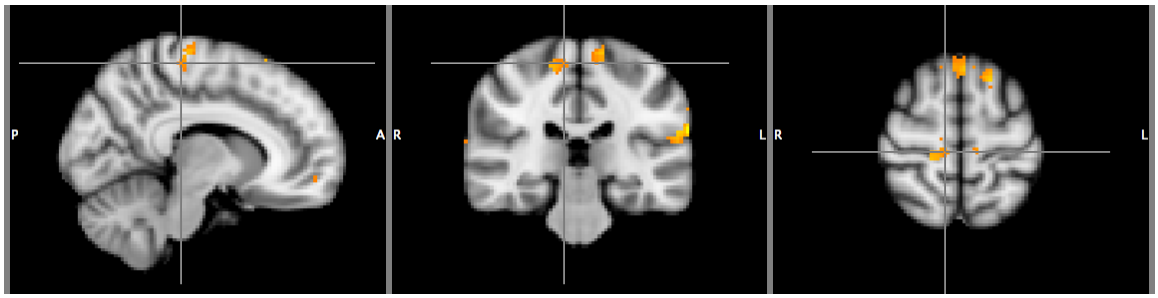


Figure 5. CIS > CIM, Flame 1, z=1.0. p <0.01; Paracentral lobule.

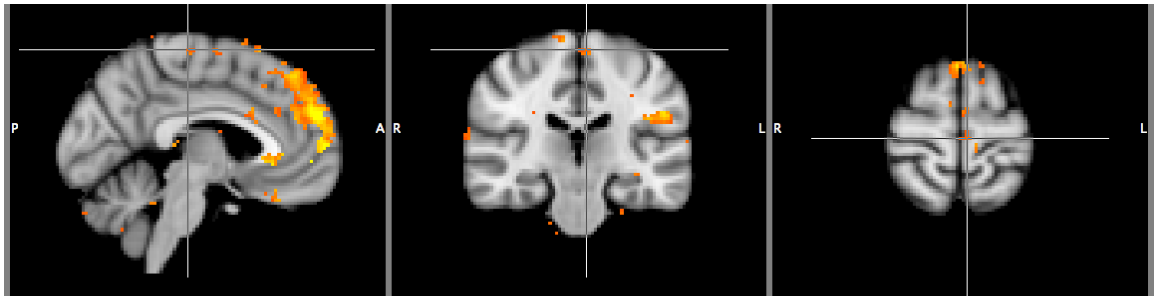


Figure 6. NIS > NIM, Flame 1, z=1.0. p <0.01; Paracentral lobule.

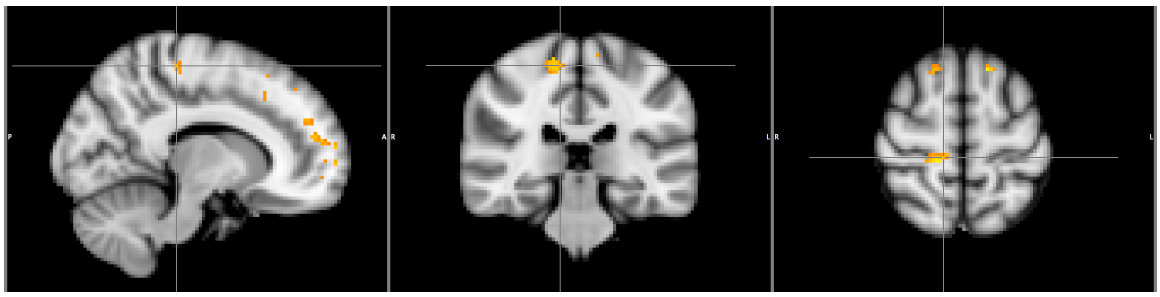


Figure 7. CIS>NIS, Flame 1, z=1.0, p <0.01; Paracentral lobule.

Primary somatosensory cortex (hand region) activations: physical stimulation conditions

CTS>CTM (clitoris touch stimulate > clitoris touch model)
NTS>NTM (nipple touch stimulate>nipple touch model)

An area corresponding to the sensory representation of the hand was activated in the left primary somatosensory cortex for all physical simulation conditions, (Figures 8 and 9). No activity in this region was noted for the imagery contrasts.

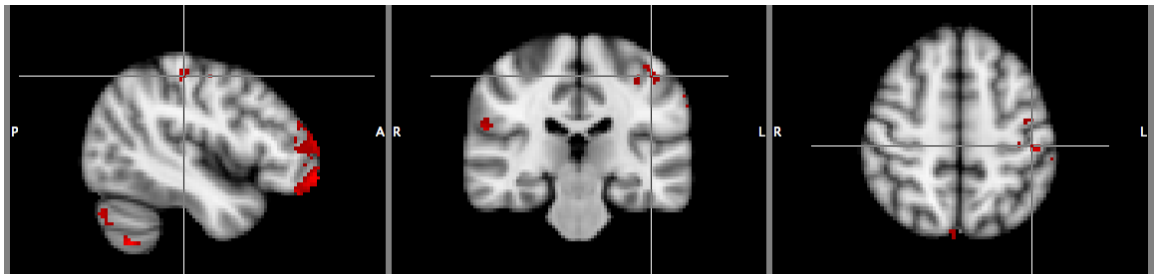


Figure 8. CTS>CTM, Flame 1, z =1.0, p < 0.01; Left BA 2.

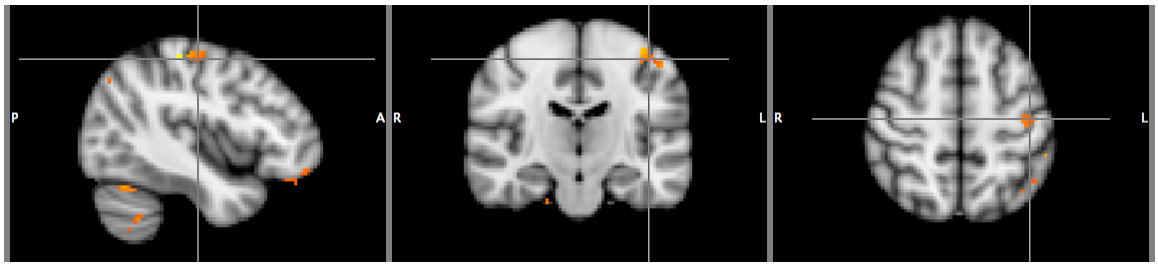


Figure 9. NTS>NTM, Flame 1, z = 1.0, p < 0.01; Left BA 3b.

Primary somatosensory cortex (hand region) activations: Contrasts between physical stimulation and imagined stimulation conditions

CTS>CIS (clitoris touch stimulate>clitoris imagine stimulate)

In a direct statistical comparison of the clitoris physical and imagined stimulation conditions, a region of greater activity is observed in the hand region of the clitoris physical stimulation condition (Figure 11).

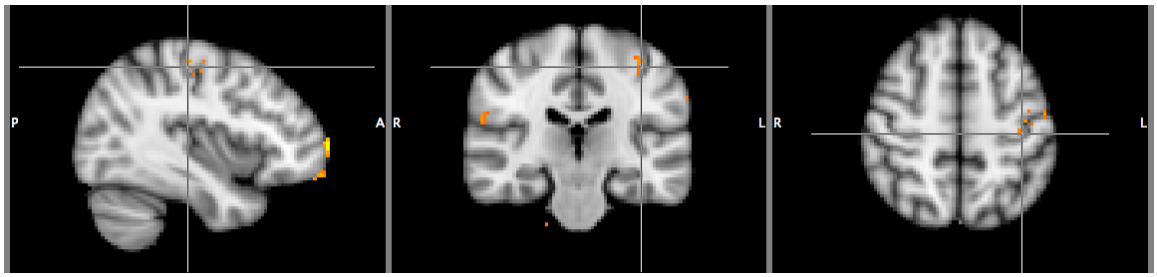


Figure 10. CTS>CIS , Flame 1, z =1.0, p < 0.01; Left BA 3.

Primary motor cortex

CTS>CIS (clitoris touch stimulate>clitoris imagine stimulate)

In a direct statistical comparison of the clitoris physical and imagined stimulation conditions, activation corresponding to the primary motor cortex is noted in the regions corresponding to hand (Figure 11).

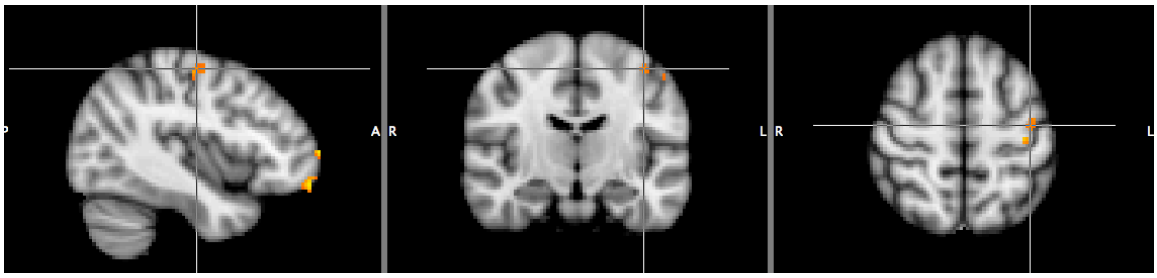


Figure 11. CTS>CIS, Flame 1, z =1.0, p < 0.01; Left BA4a.

Secondary somatosensory cortex activations: physical stimulation conditions

CTS>CTM (clitoris touch stimulate > clitoris touch model)
NTS>NTM (nipple touch stimulate>nipple touch model)

Activation of the secondary somatosensory cortex (parietal operculum OP1 R) was observed in the clitoris physical stimulation condition (Figure 12). No activity in the partial operculum was observed for physical nipple stimulation.

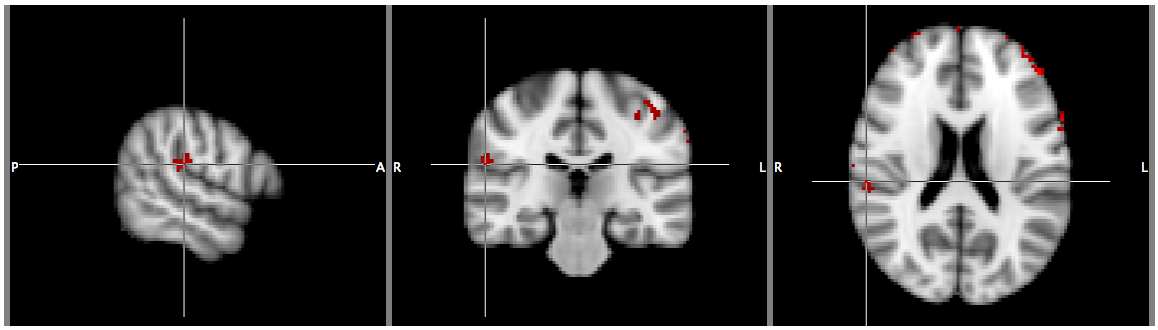


Figure 12. CTS>CTM, Flame 1, z = 1.0, p < 0.01; Right OP1.

Secondary somatosensory cortex activations: Imagined stimulation conditions

CIS>CIM (clitoris imagine stimulate > clitoris imagine model)
NIS>NIM (nipple imagine simulate > nipple imagine model)

Imagined stimulation of the clitoris and nipple similarly activated the parietal operculum in area OP4 left (Figures 13 and 14).

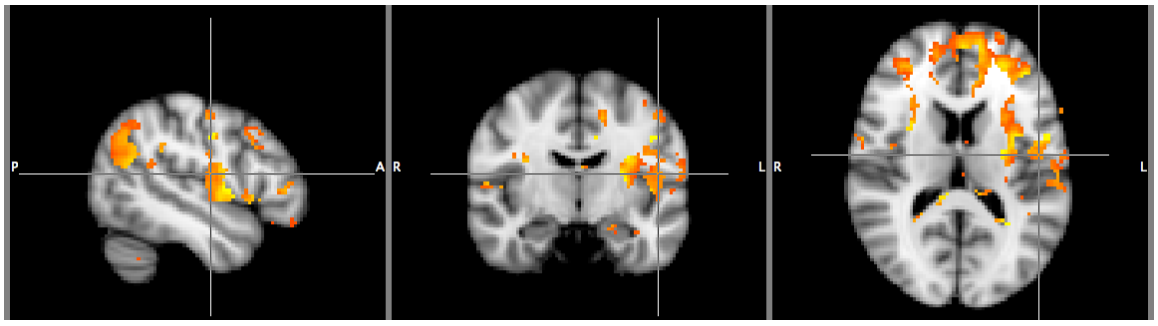


Figure 13. CIS>CIM, Flame 1, z = 1.0, p < 0.01; Left OP4.

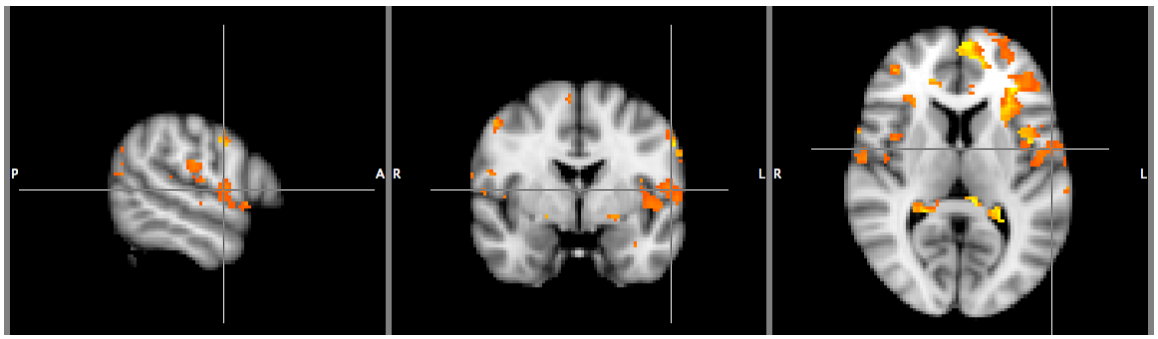


Figure 14. NIS>NIM, Flame 1, z = 1.0, p < 0.01; Left OP4.

Secondary somatosensory activations: Contrasts between physical stimulation and imagined stimulation conditions

CTS>CIS (clitoris touch stimulation > clitoris imagine stimulation)

In the results of a direct comparison of the clitoris physical stimulation condition and the imagined stimulation condition (Figure 15), a region of greater activity in OP1 on the right side was observed.

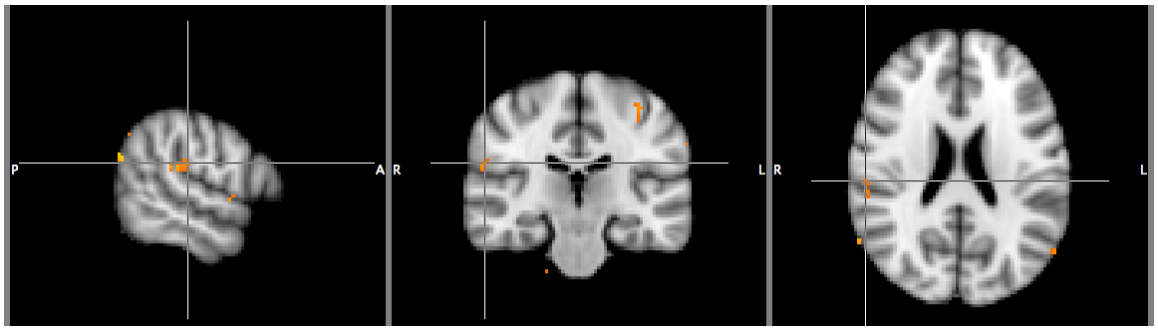


Figure 15. CTS>CIS, Flame 1, z = 1.0, p < 0.01; Right OP1.

Cerebellum activations: Physical stimulation conditions
CTS>CTM (clitoris touch stimulate > clitoris touch model)
NTS>NTM (nipple touch stimulate>nipple touch model)
CTS> NTS (clitoris touch stimulate> nipple touch stimulate
NTS>CTS (nipple touch stimulate> clitoris touch stimulate)

A similar pattern of predominantly right-sided cerebellar activation is observed in both the clitoris and nipple physical stimulation conditions, (Figures 16 and 17). When the clitoris and nipple contrasts are directly contrasted, there is overall more activity on the right side of the cerebellum for the clitoris stimulation condition, and more activity on the left for the nipple stimulation condition (Figures 18 and 19).

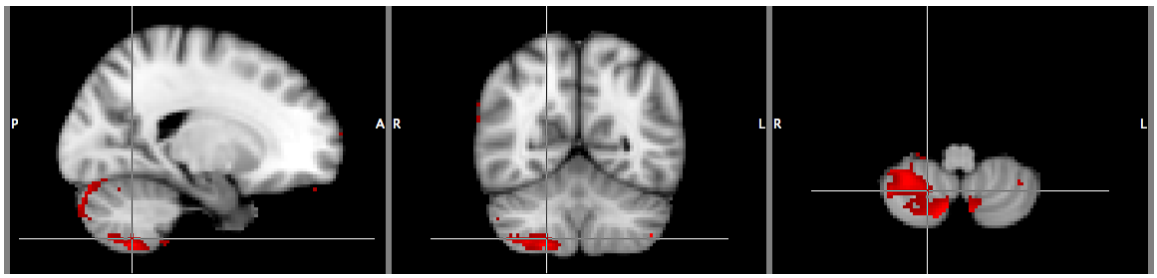


Figure 16. CTS>CTM, Flame 1, z = 1.0, p , 0.01; Right cerebellum.

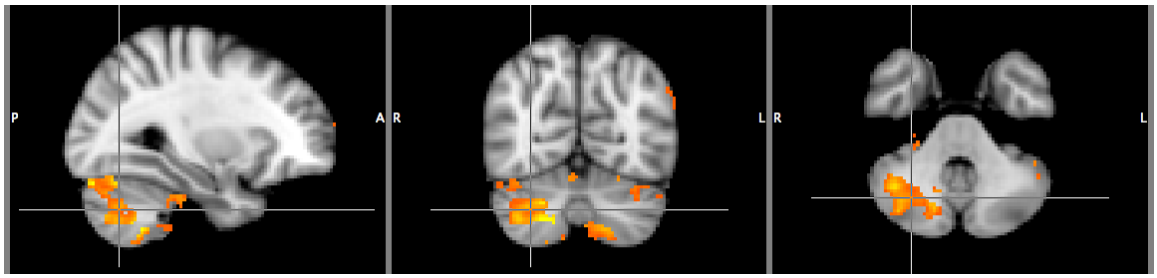


Figure 17. NTS>NTM, Flame 1, z = 1.0, p < 0.01; Right cerebellum.

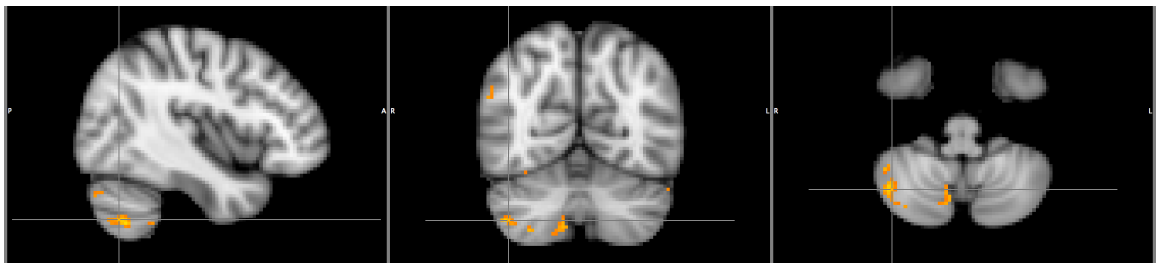


Figure 18. CTS>NTS, Flame 1, z = 1.0, p < 0.01; Right cerebellum.

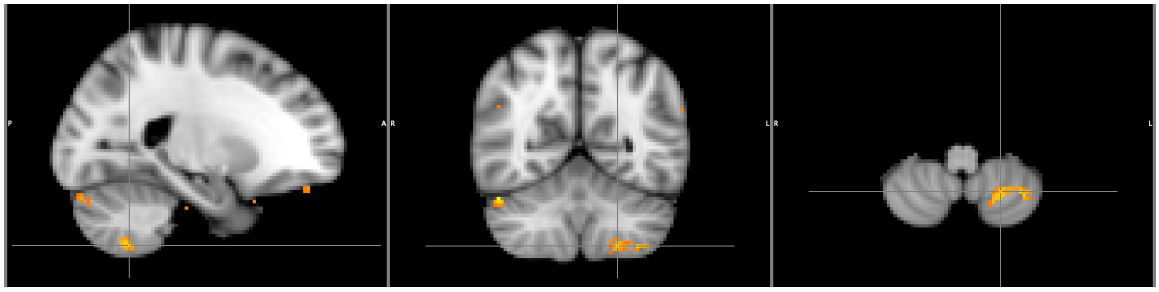


Figure 19. NTS>CTS, Flame 1, z = 1.0, p < 0.01; Left cerebellum.

Cerebellum activations: Imagined stimulation conditions
CIS>CIM (clitoris imagine stimulate > clitoris imagine model)
NIS>NIM (nipple imagine simulate > nipple imagine model)

Cerebellar activations are also noted for the imagined stimulation contrasts, with more activity on the right side for imagined clitoris stimulation, (Figure 20) and bilateral cerebellar activity noted for the imagined nipple stimulation (Figure 21)

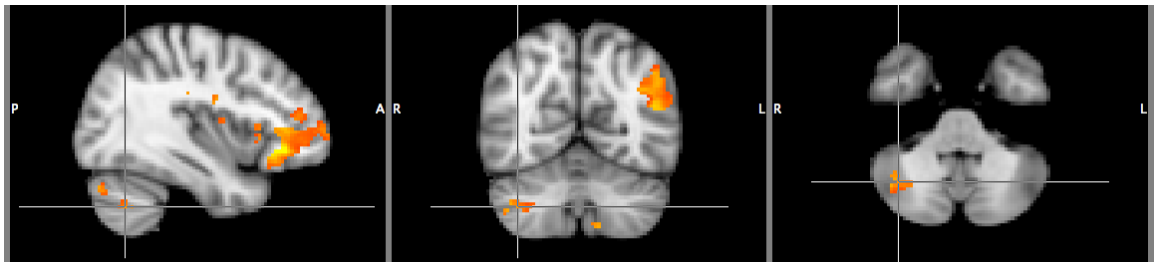


Figure 20. CIS>CIM, Flame 1, z = 1.0, p < 0.01; Right cerebellum.

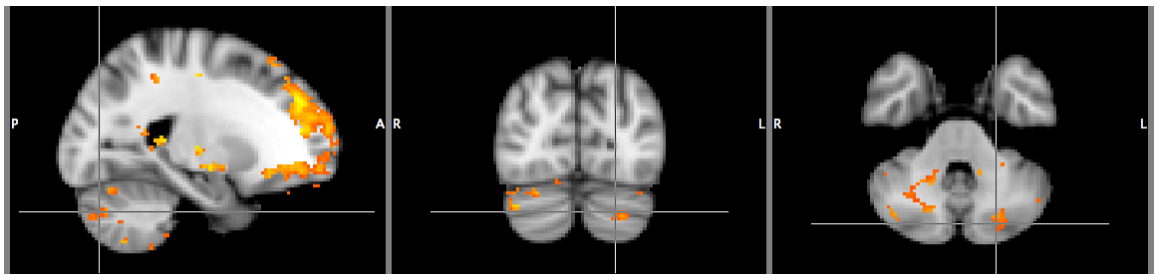


Figure 21. NIS>NIM, Flame 1, z = 1.0, p < 0.01; Bilateral cerebellum.

Cerebellum activations: Contrasts between physical stimulation and imagined stimulation conditions

CTS>CIS (clitoris touch stimulate> clitoris imagine stimulate)
NTS>NIS (nipple touch stimulate > nipple imagine stimulate)
CTS/NTS>CIS/NIS (physical conditions>imagery conditions)

Direct statistical comparison of the physical and imagined stimulation contrasts for the clitoris (Figure 22) and nipple conditions (Figure 23) indicate significantly more activity in the right cerebellum for the physical stimulation conditions. When the conditions are collapsed such that data for clitoris and nipple physical stimulation are combined and compared statistically with the combined clitoris and nipple imagined stimulation data, the results of that contrast indicate greater activity of the right cerebellum in the physical stimulation conditions (Figure 24).

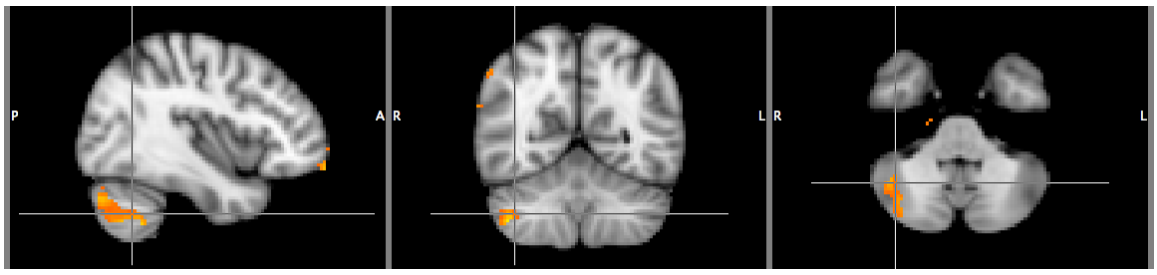


Figure 22. CTS>CIS, Flame 1, z = 1.0, p < 0.01; Right cerebellum.

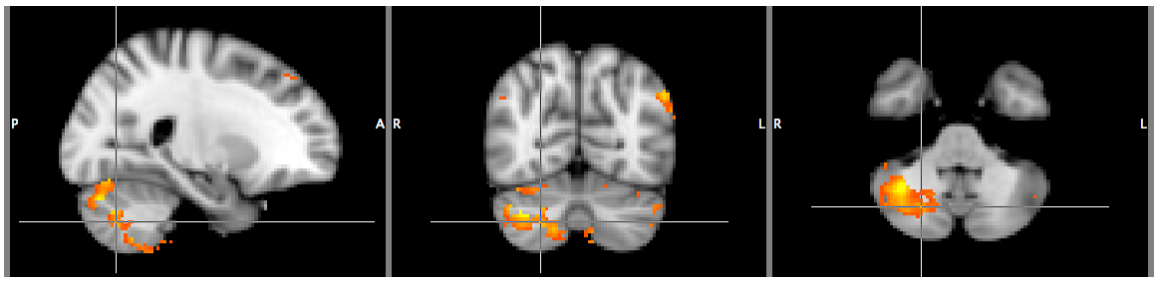


Figure 23. NTS>NIS, Flame 1, z = 1.0, p < 0.01; Right cerebellum.

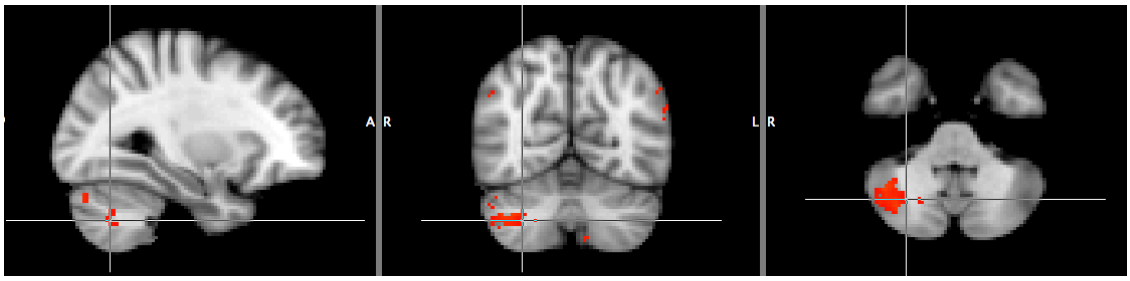


Figure 24. CTS/NTS>CIS/NIS, Flame 1, z = 1.0, p < 0.01; Right cerebellum.

Frontal cortex activation: Physical stimulation conditions
CTS>CTM (clitoris touch stimulate > clitoris touch model)
NTS>NTM (nipple touch stimulate>nipple touch model)

Frontal pole activation is noted in the clitoris physical stimulation contrast (Figure 25), with less observed in the nipple physical stimulation condition (Figure 26).

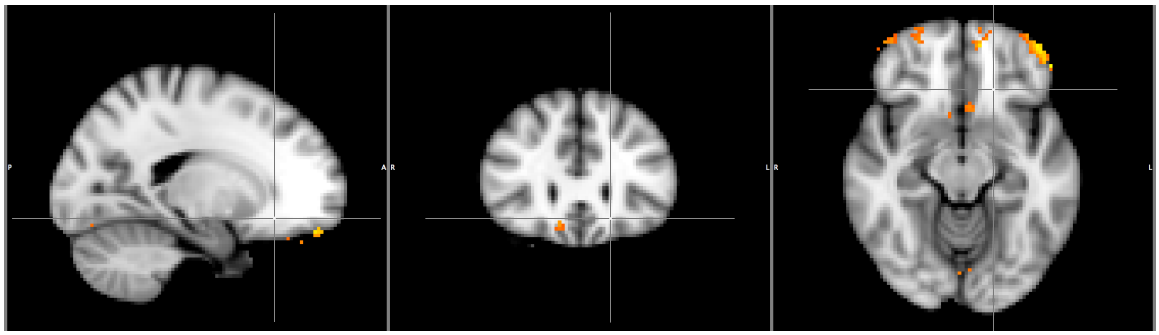


Figure 25. CTS>CTM, Flame 1, z = 1.0, p < 0.01; Frontal cortex.

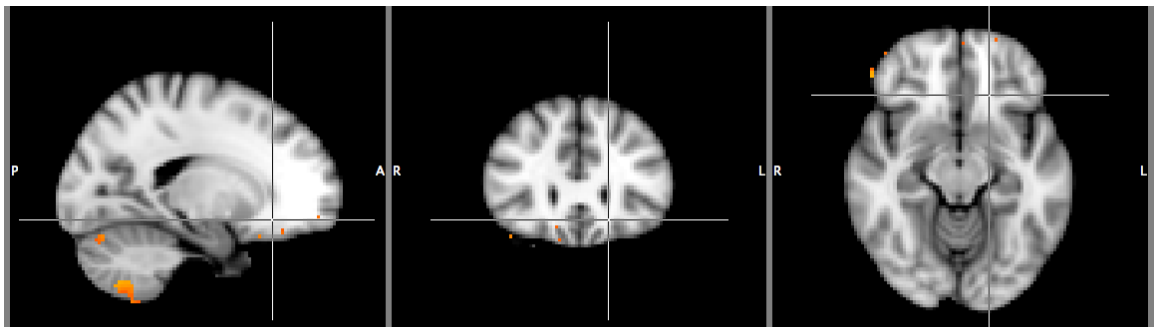


Figure 26. NTS>NTM, Flame 1, z = 1.0, p < 0.01; Frontal cortex.

Frontal cortex activation: Imagined stimulation conditions
CIS>CIM (clitoris imagine stimulate > clitoris imagine model)
NIS>NIM (nipple imagine simulate > nipple imagine model)

Activations are observed in the orbital frontal cortex, frontal pole, frontal medial cortex, superior frontal gyrus, inferior frontal gyrus, dorsolateral prefrontal cortex, and anterior cingulate gyrus for clitoris imagine stimulation (Figure 27), with a similar pattern, with less overall activity, noted for nipple imagine stimulation (Figure 28). In general, there appears to be more overall activity on the left side of the frontal regions.

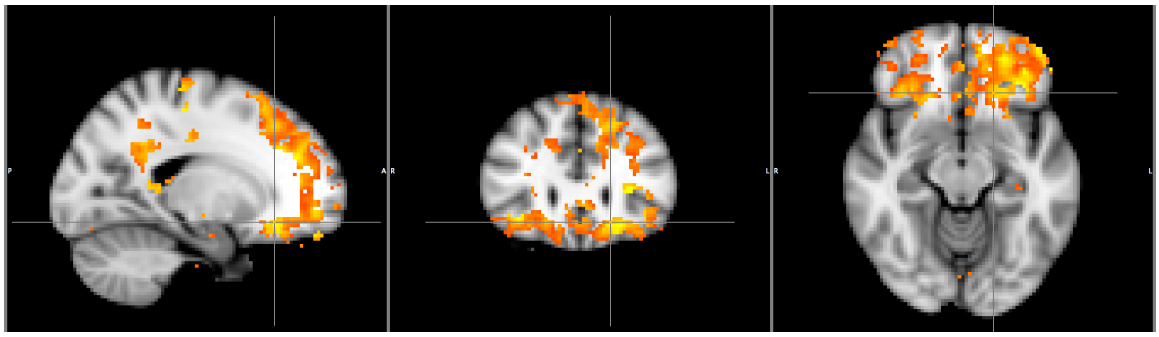


Figure 27. CIS>CIM, Flame 1, z = 1.0, p < 0.01; Frontal cortex.

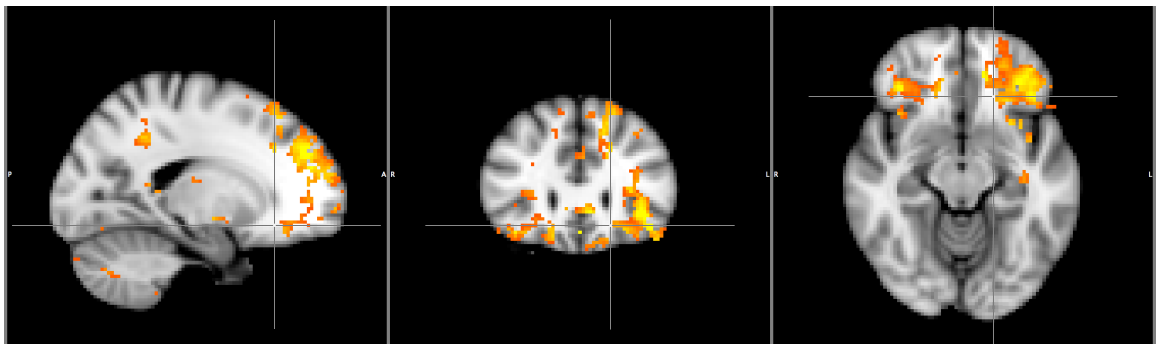


Figure 28. NIS>NIM, Flame 1, z = 1.0, p < 0.01; Frontal cortex.

Frontal cortex activations: Contrasts between physical stimulation and imagined stimulation conditions

CIS>CTS (clitoris imagine stimulation > clitoris touch stimulation)
NIS>NTS (nipple imagine stimulation> nipple touch stimulation)
CIS/NIS>CTS/NTS (imagery stimulation>physical stimulation)

Direct statistical analysis of clitoris imagined stimulation greater than clitoris physical stimulation (Figure 29) indicates small regions of activation in the frontal medial cortex, frontal pole, and the superior frontal gyrus, predominantly on the left side. When nipple imagined stimulation is similarly compared to nipple physical stimulation (Figure 30), the resulting contrast indicates activation of a small region of the left frontal pole. And finally, when the data are collapsed across conditions for imagery and physical stimulation (Figure, 31) the resulting contrast indicates greater activity of the left orbital frontal cortex and frontal pole in the imagery conditions.

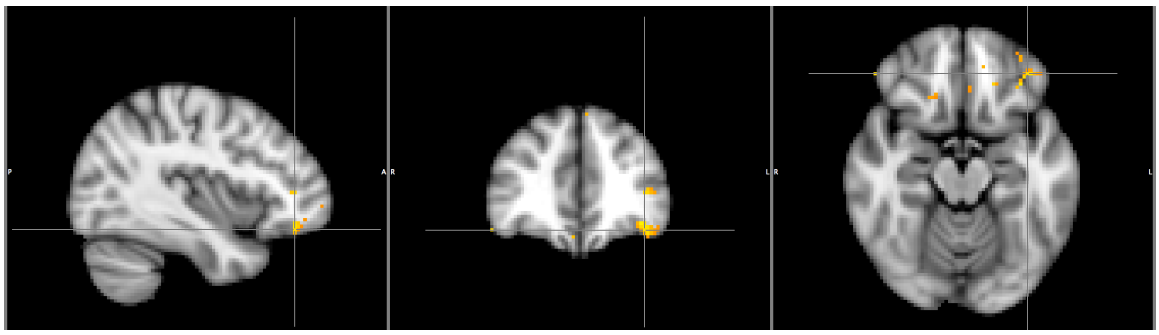


Figure 29. CIS>CTS, Flame 1, z = 1.0, p < 0.01; Frontal activations, left side.

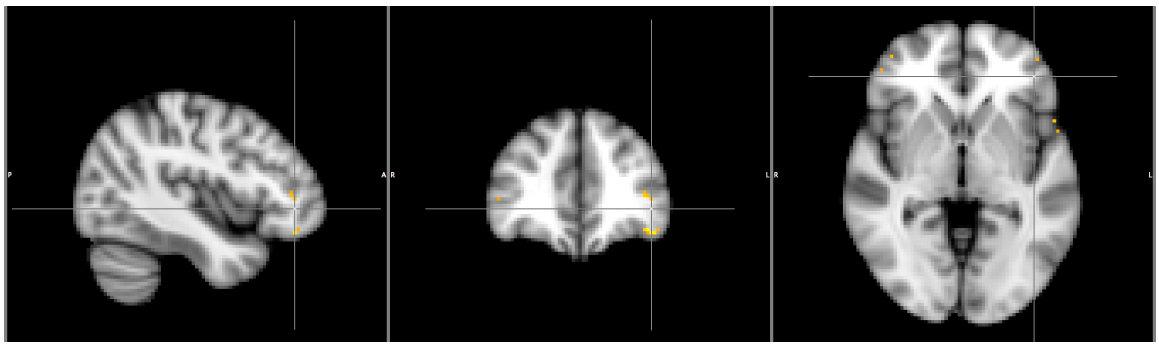


Figure 30. NIS>NTS, Flame 1, z = 1.0, p < 0.01; Frontal pole, left.

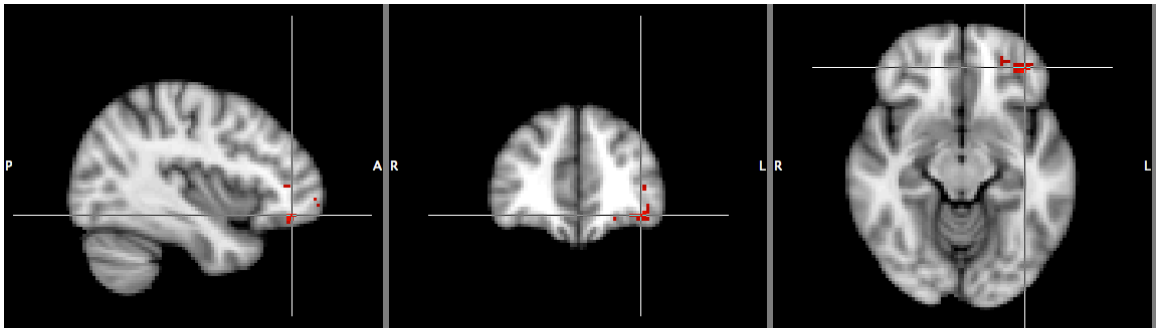


Figure 31. CIS/NIS>CTS/NTS, Flame 1, z = 1.0, p < 0.01; OFC and frontal pole left.

Activations only present in imagined stimulation conditions
Insular cortex
CIS>CIM (clitoris imagine stimulate > clitoris imagine model)
NIS>NIM (nipple imagine simulate > nipple imagine model)

Activations of the insular cortex were observed only in the imagined stimulation conditions, with the left insula activated in the clitoris imagined stimulation contrast (Figure 32), and bilateral activation noted in the nipple imagined stimulation contrast (Figure 33).

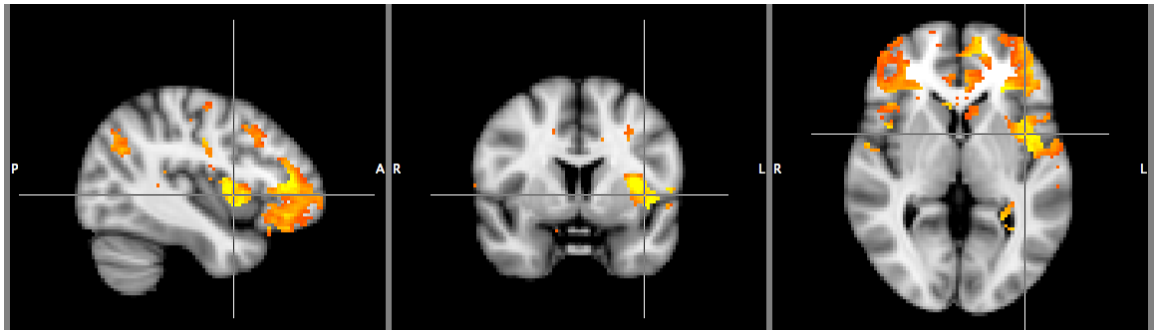


Figure 32. CIS>CIM, Flame 1, z = 1.0, p < 0.01; Left insula.

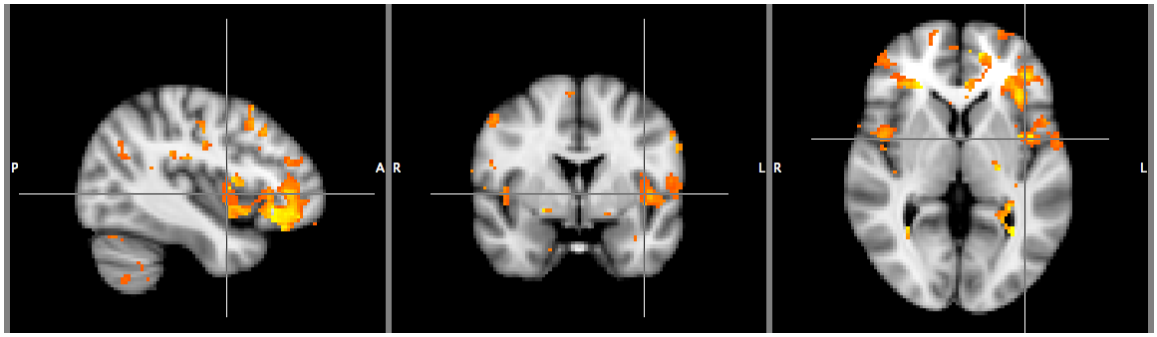


Figure 33. NIS>NIM, Flame 1, z = 1.0, p < 0.01; Bilateral insula.

Amygdala and hippocampus
CIS>CIM
NIS> NIM

Activation of the left amygdala was observed for imagined clitoris stimulation (Figure 34) and imagined nipple stimulation (Figure 35). In addition, activation of the left hippocampus was noted in the nipple imagery condition. No activation of these regions was noted in the physical stimulation contrasts.

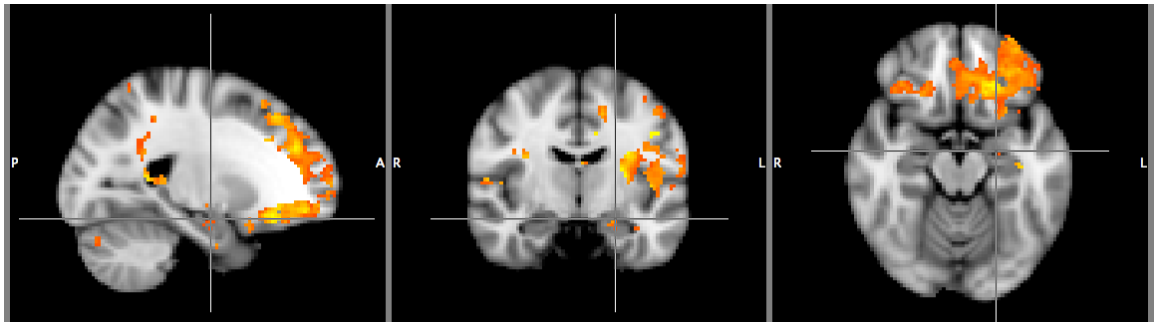


Figure 34. CIS> CIM, Flame 1, z = 1.0, p < 0.01; Left amygdala.

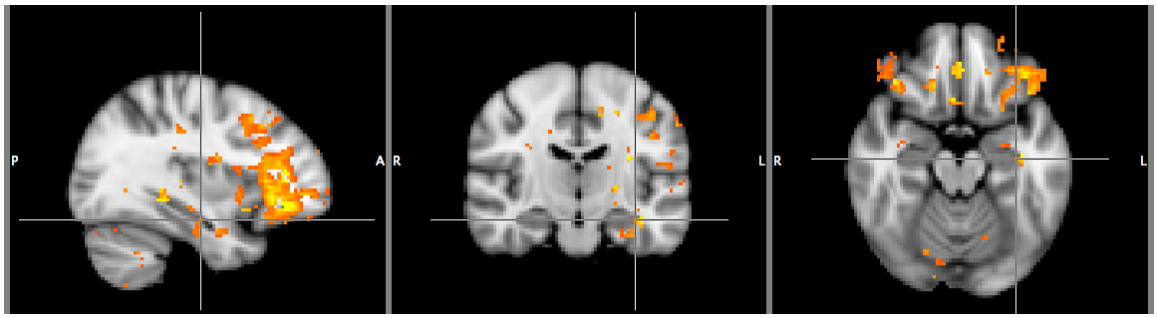


Figure 35. NIS>NIM, Flame 1, z = 1.0, p < 0.01; Left amygdala and hippocampus.

Inferior parietal lobule
CIS>CIM
CIS>CTS

A region of activation of the left inferior parietal lobule was observed in the clitoris imagined stimulation contrast (Figure 36). A small amount of activation of this region is observed when the imagined clitoris stimulation is statistically compared to the physical stimulation condition (Figure 37).

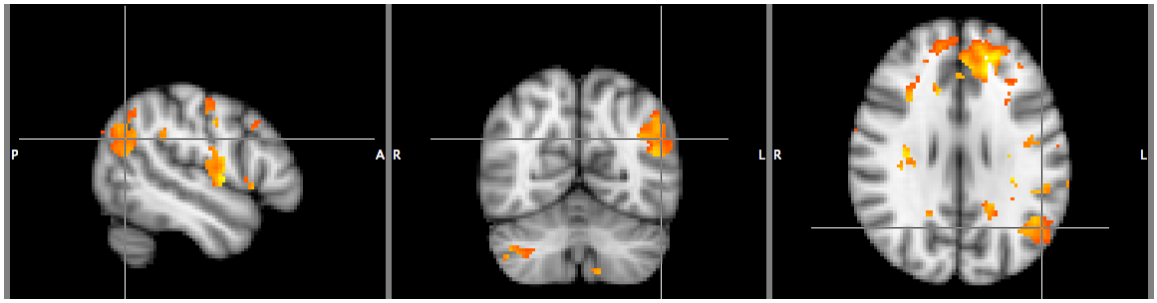


Figure 36. CIS>CIM, Flame 1, z = 1.0, p < 0.01; Left IPL.

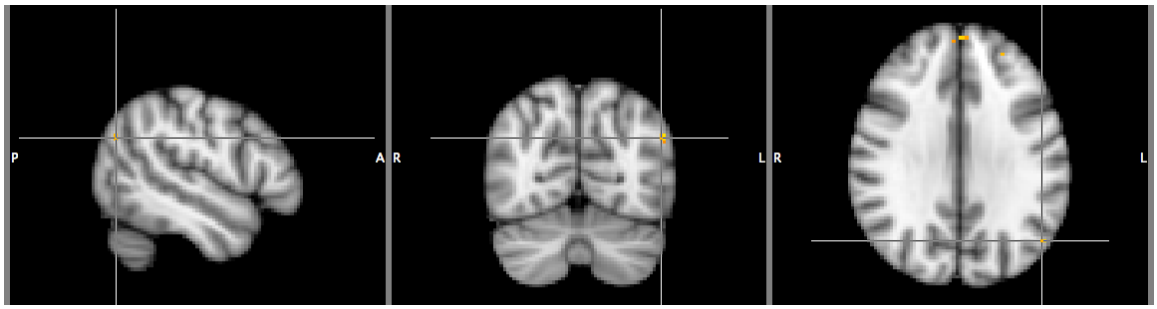


Figure 37. CIS>CTS, Flame 1, z = 1.0, p < 0.01; Left IPL.

Appendix E. Additional orgasm results

Self-induced orgasm compared with partner-induced orgasm

Mid Stimulation > Early Stimulation

The results were significant for the self group and the contrast self > partner.

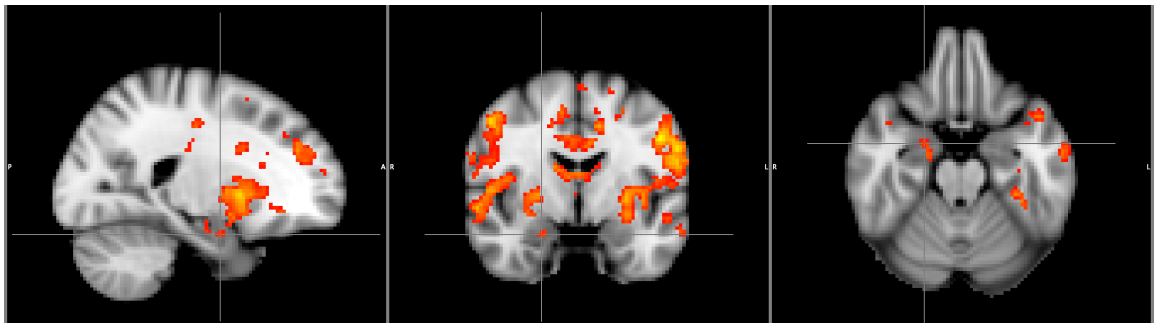


Figure 1. Self group mean; Flame 1, Cluster 1.65, p<0.05, Right amygdala.

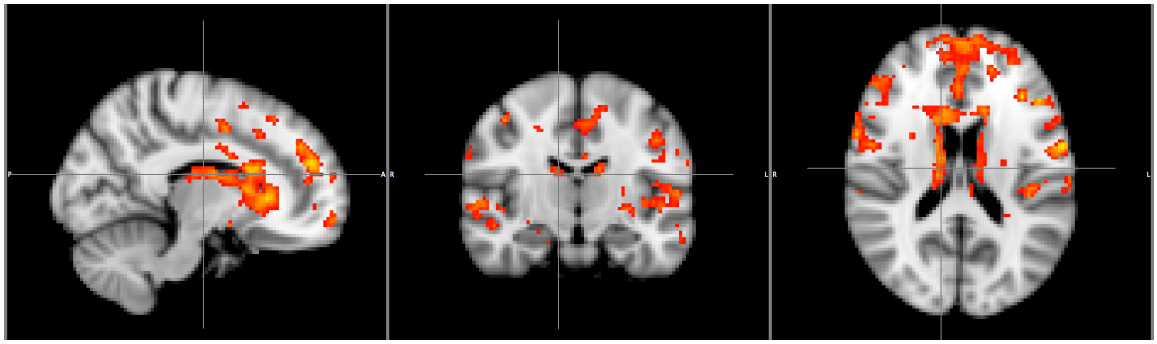


Figure 2. . Self group mean; Flame 1, Cluster 1.65, p<0.05, Bilateral thalamus.

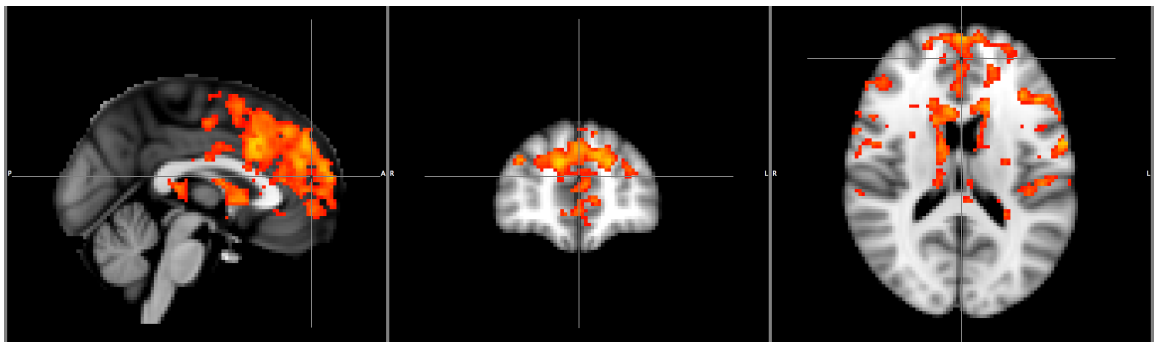


Figure 3. Self group mean; Flame 1, Cluster 1.65, p<0.05, Prefrontal cortex.

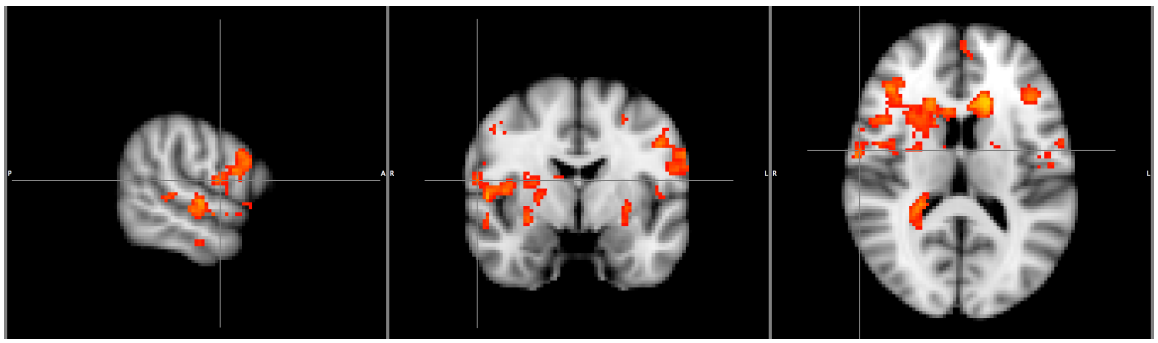


Figure 4. Self>Partner; Flame 1, Cluster 1.65, p<0.05, Right OP 4.

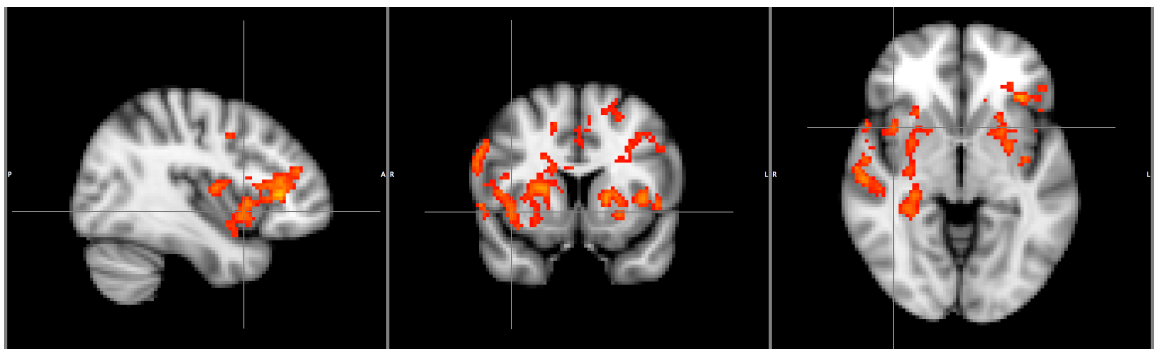


Figure 5. Self>Partner; Flame 1, Cluster 1.65, p<0.05, Right insula.

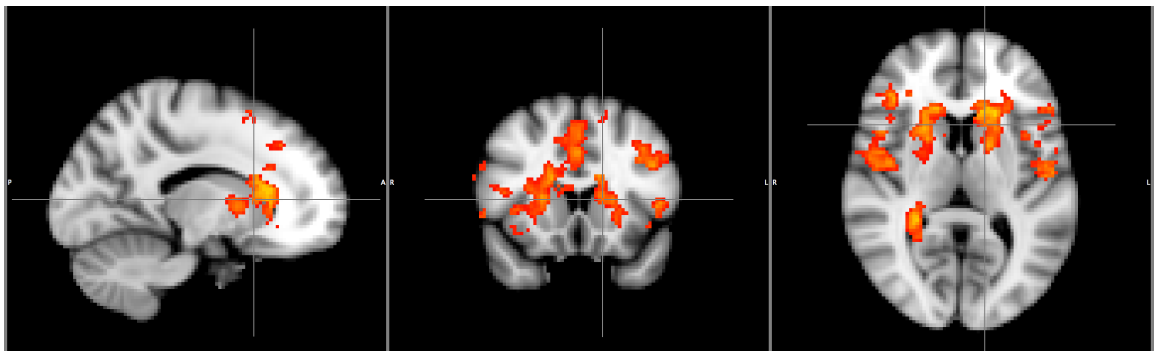


Figure 6. Self>Partner; Flame 1, Cluster 1.65, p<0.05, Bilateral caudate.

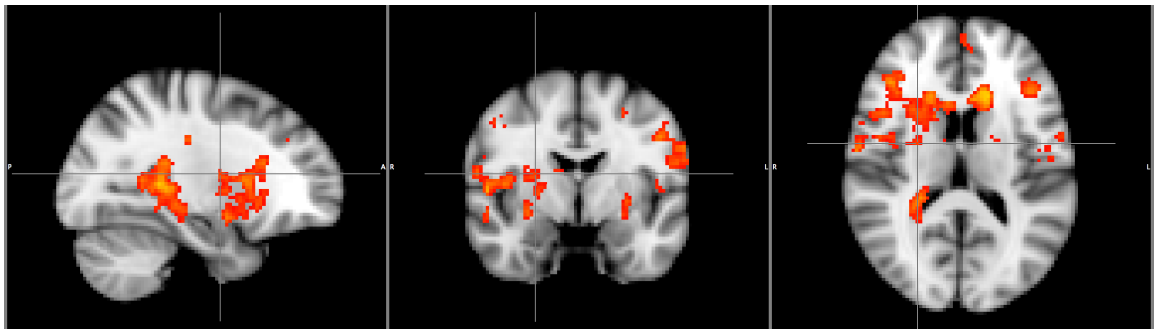


Figure 7. Self>Partner; Flame 1, Cluster 1.65, p<0.05, Right putamen.

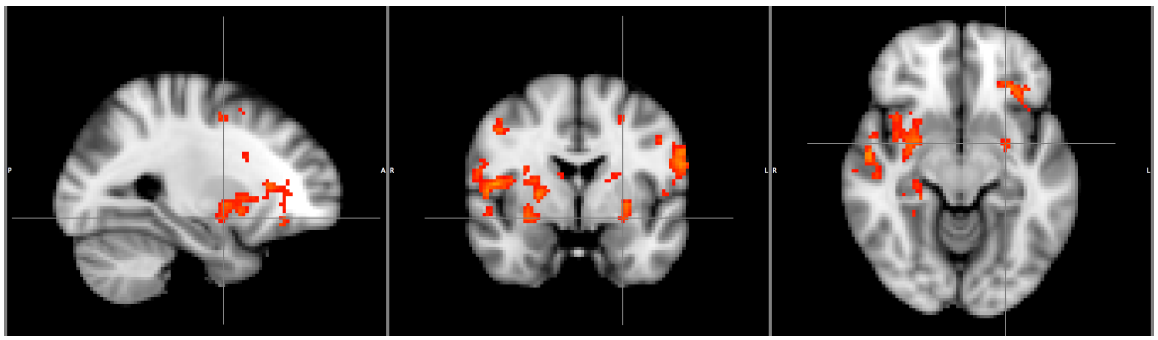


Figure 8. Self>Partner; Flame 1, Cluster 1.65, p<0.05, Left amygdala.

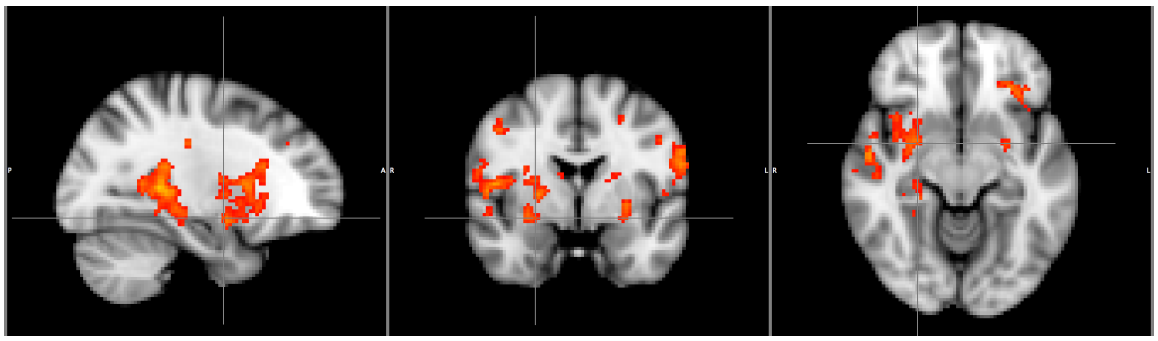


Figure 9. Self>Partner; Flame 1, Cluster 1.65, p<0.05, Right amygdala.

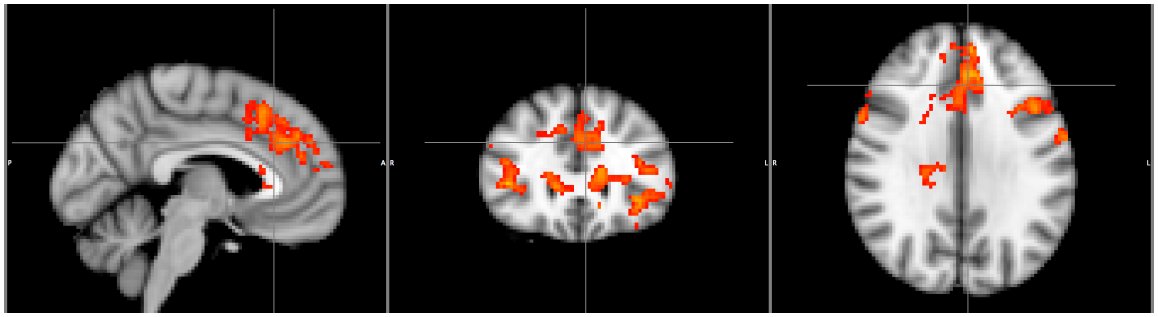


Figure 10. Self>Partner; Flame 1, Cluster 1.65, p<0.05, IFG and Anterior Cingulate Cortex.

Late Stimulation > Mid Stimulation

There were significant results for the partner group mean and the contrast, partner > self.

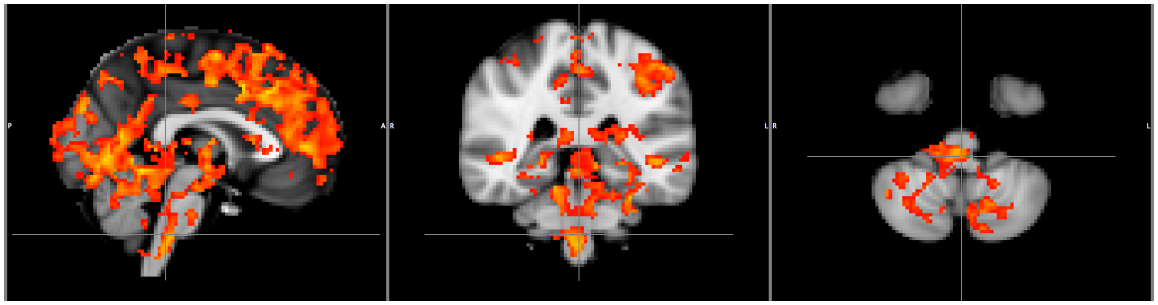


Figure 11. Partner group mean; Flame 1, Cluster 1.65, p<0.05, Brainstem and widespread activations.

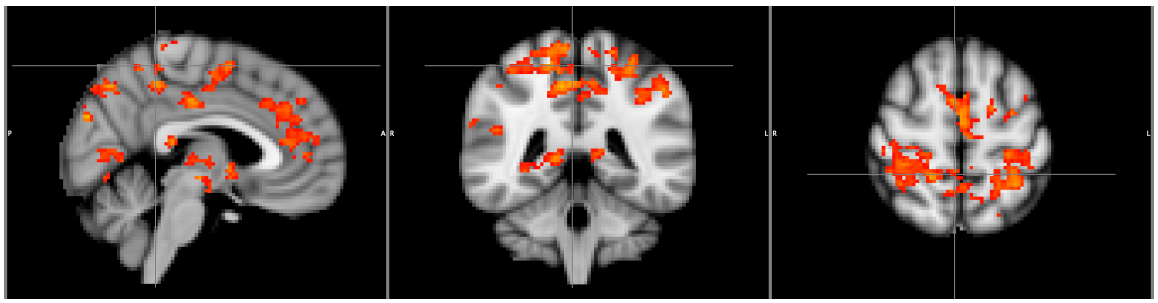


Figure 12. Partner>Self; Flame 1, Cluster 1.65, p<0.05, Paracentral lobule.

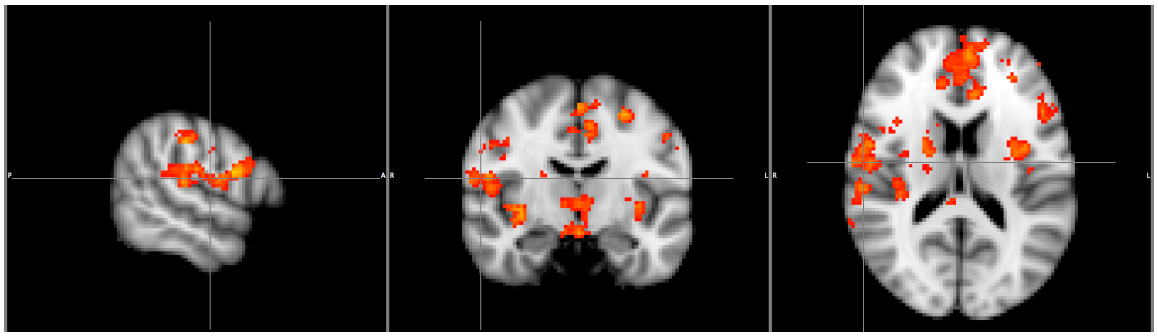


Figure 13. Partner>Self; Flame 1, Cluster 1.65, p<0.05, OP4 Right.

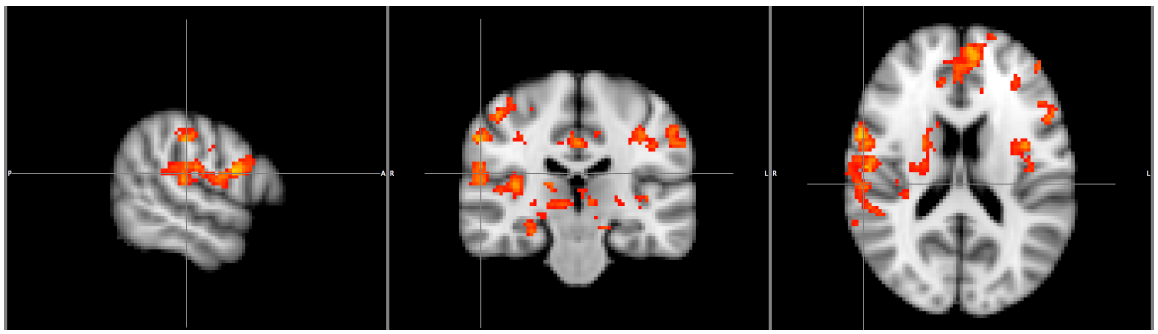


Figure 14. Partner>Self; Flame 1, Cluster 1.65, p<0.05, OP1 Right.

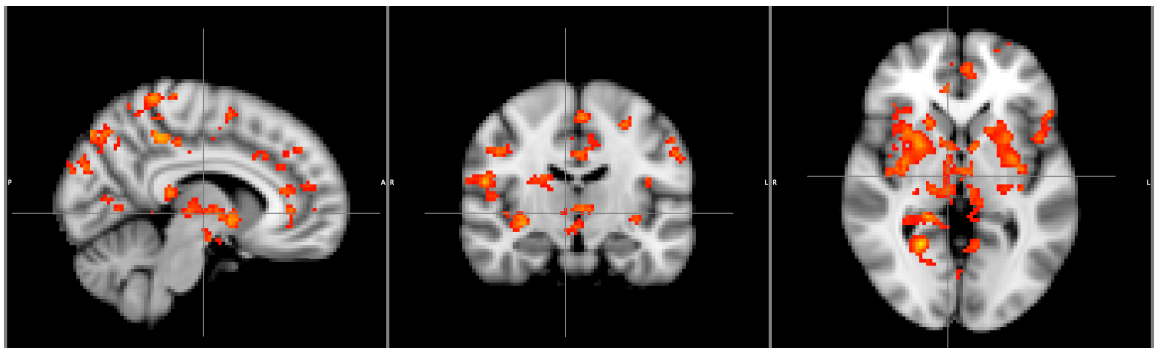


Figure 15. Partner>Self; Flame 1, Cluster 1.65, p<0.05, Right thalamus.

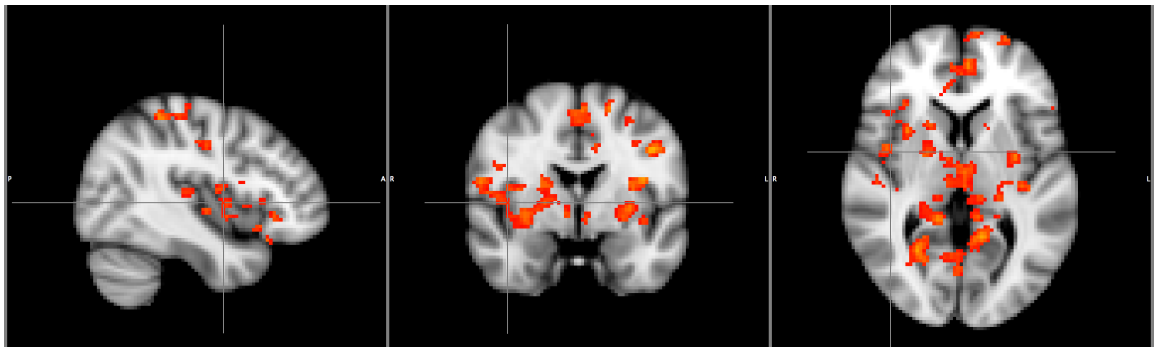


Figure 16. Partner>Self; Flame 1, Cluster 1.65, p<0.05, Right insula.

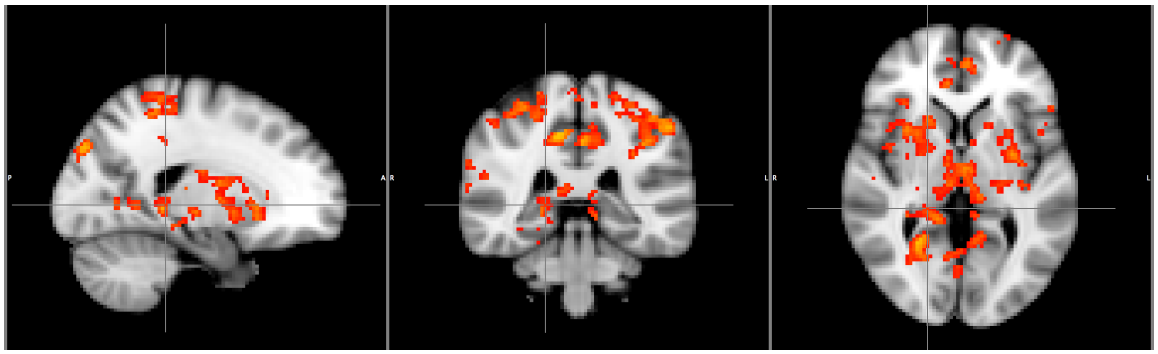


Figure 17. Partner>Self; Flame 1, Cluster 1.65, p<0.05, Right hippocampus.

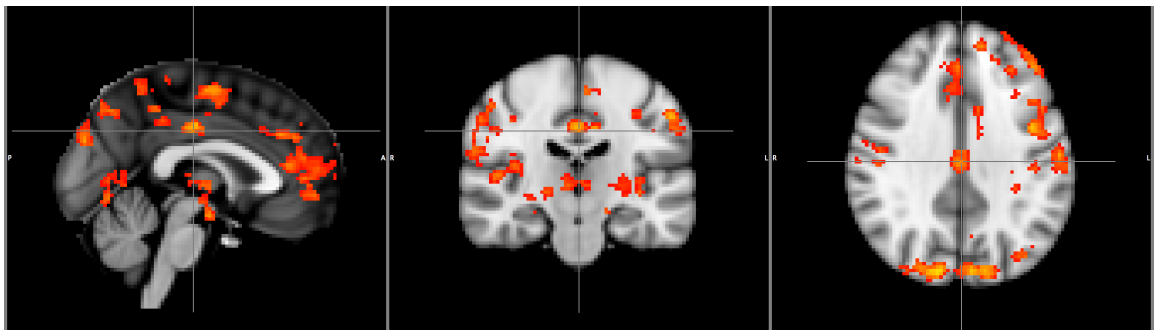


Figure 18. Partner>Self; Flame 1, Cluster 1.65, p<0.05, Posterior cingulate cortex.

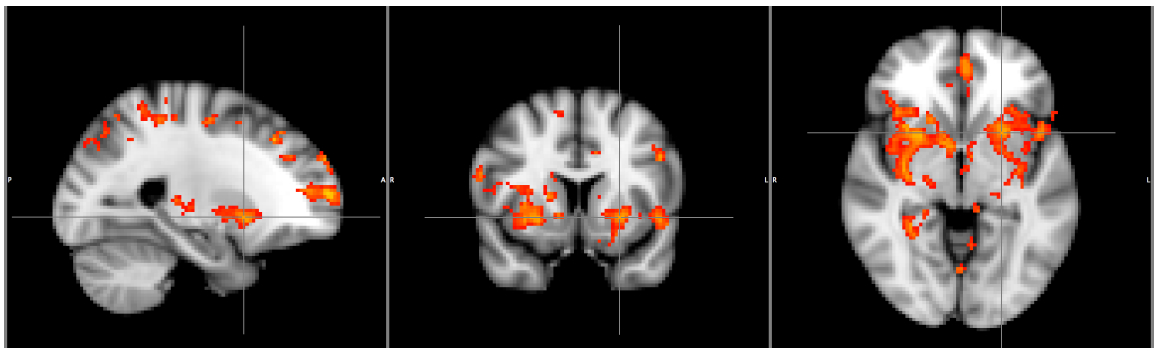


Figure 19. Partner>Self; Flame 1, Cluster 1.65, p<0.05, Bilateral putamen.

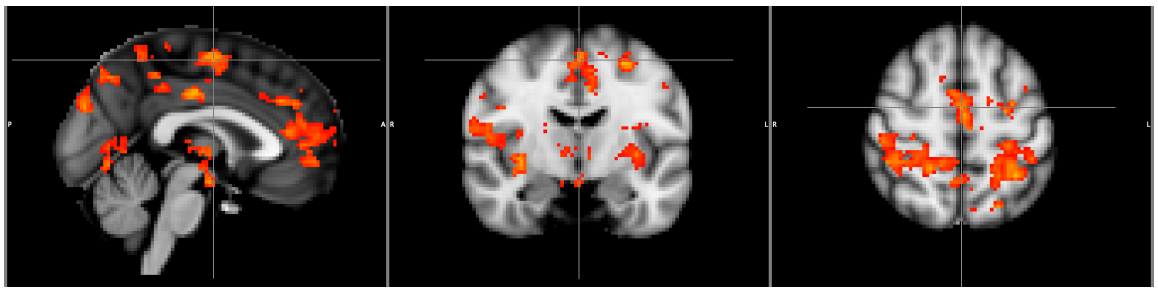


Figure 20. Partner>Self; Flame 1, Cluster 1.65, p<0.05, Premotor cortex.

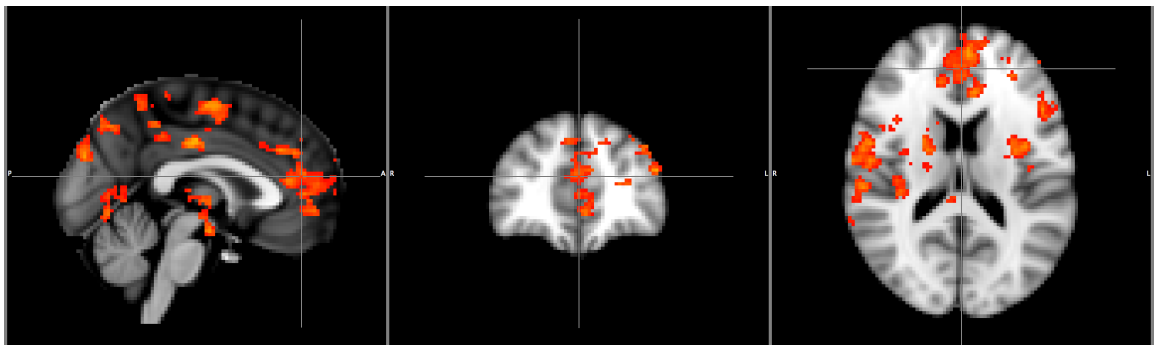


Figure 21. Partner>Self; Flame 1, Cluster 1.65, p<0.05, Medial prefrontal cortex.

Orgasm > Mid Stimulation

There were no significant results for the contrasts self>partner, partner> self. The only significant result was for the partner group mean.

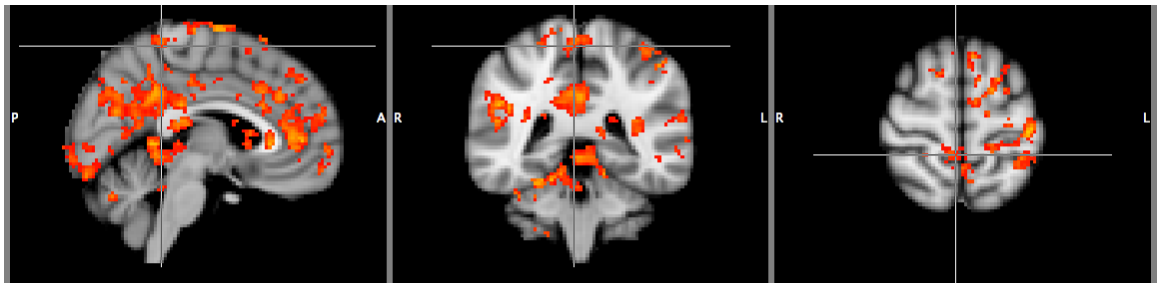


Figure 22. Partner group mean: Flame 1, Cluster 1.65, p <0.05, Paracentral lobule.

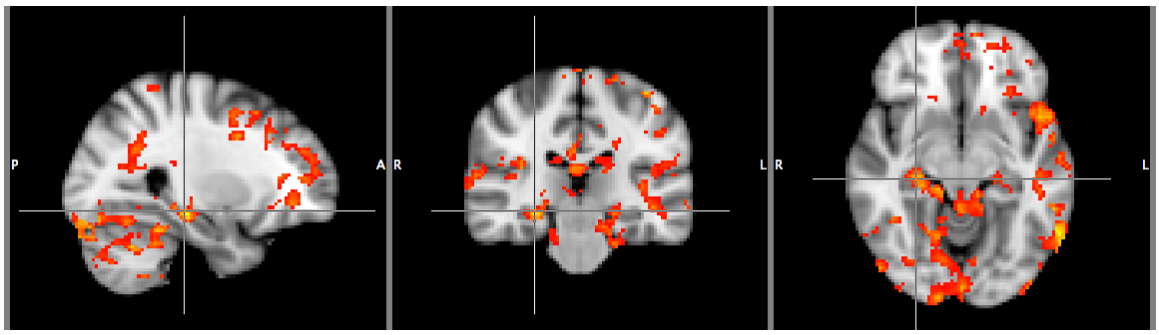


Figure 23. Partner group mean: Flame 1, Cluster 1.65, p <0.05, Right hippocampus.

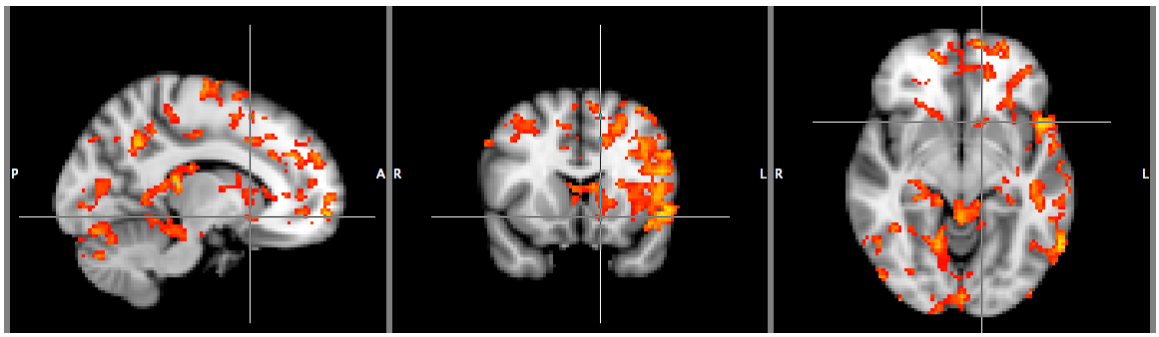


Figure 24. Partner group mean: Flame 1, Cluster 1.65, p <0.05, Left nucleus accumbens.

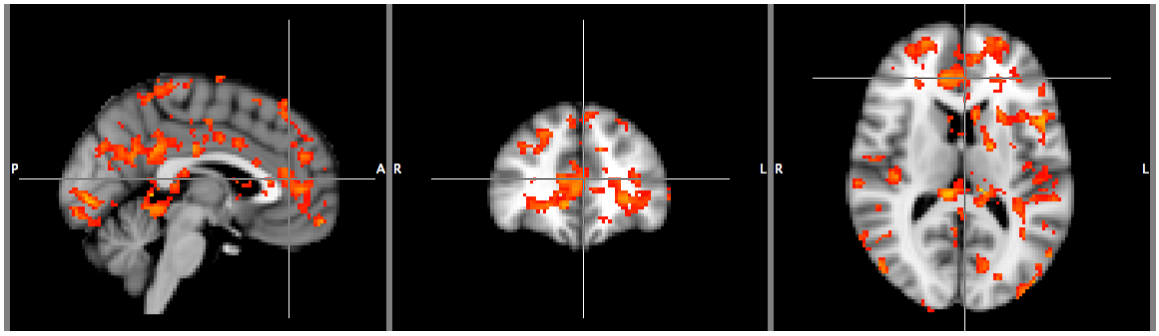


Figure 25. Partner group mean: Flame 1, Cluster 1.65, p <0.05, Anterior cingulate cortex and medial prefrontal cortex.

Orgasm > Late Stimulation

The only significant result was for the self group mean.

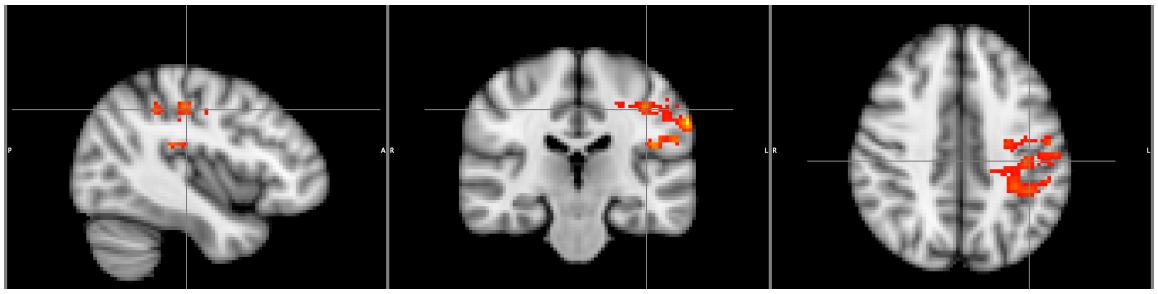


Figure 26. Self group mean: Flame 1, Cluster 1.65, p <0.05, Left BA3b.

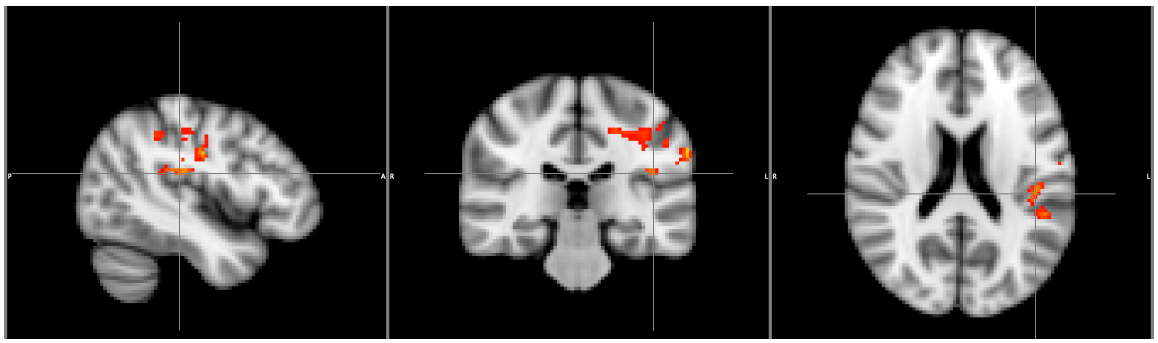


Figure 27. Partner group mean: Flame 1, Cluster 1.65, p <0.05, OP1 left.

Orgasm > Early Recovery

There were no significant differences between group. The results for both self and partner group means were significant.

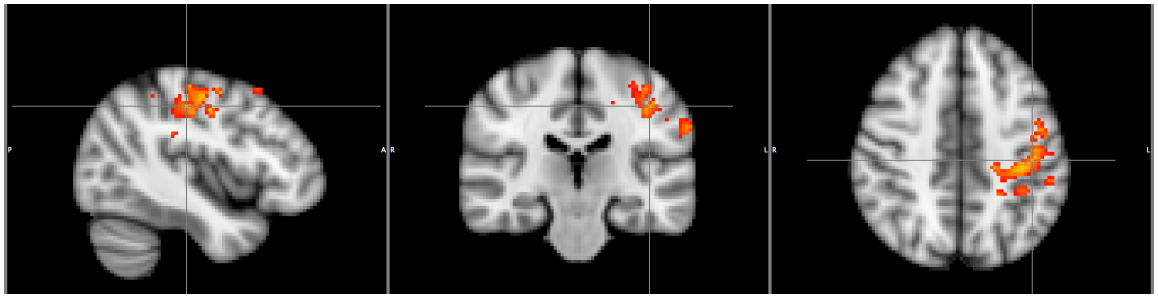


Figure 28 . Self group mean; Flame 1, Cluster 1.65, p <0.05, BA3b Left.

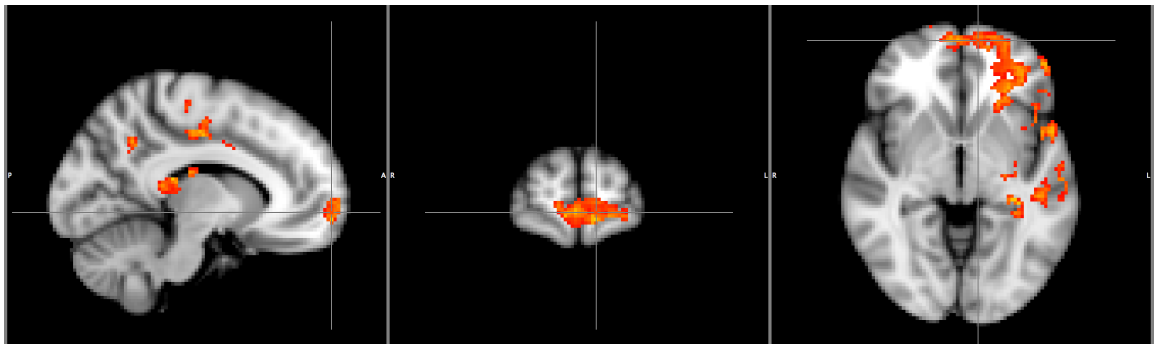


Figure 29. Partner group mean; Flame 1, Cluster 1.65, p <0.05, Prefrontal cortex.

Early Recovery > Late Recovery

Only the Partner group mean was significant.

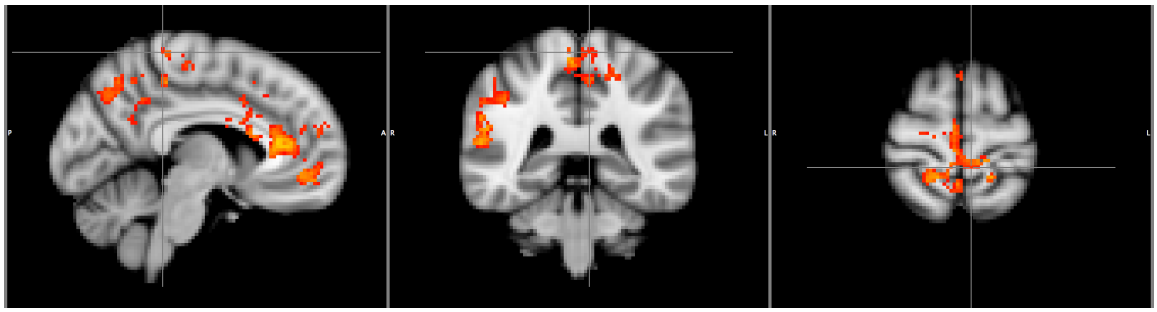


Figure 30. Partner group mean; Flame 1, Cluster 1.65, p <0.05, Paracentral lobule.

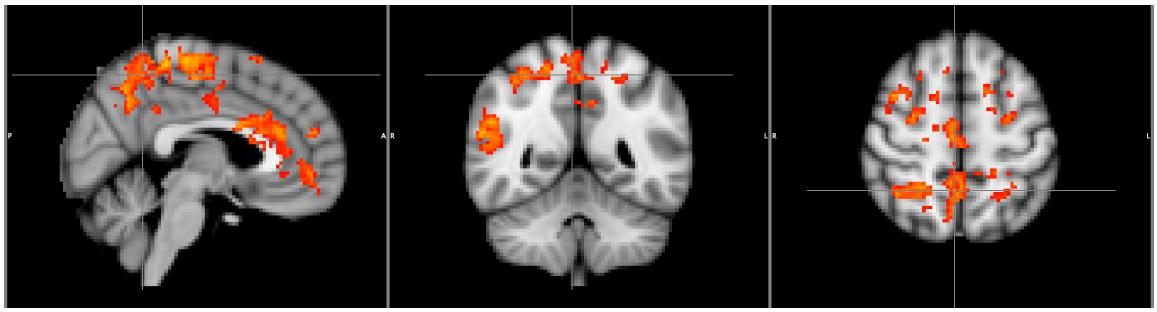


Figure 31. Partner group mean; Flame 1, Cluster 1.65, p <0.05, Precuneus.

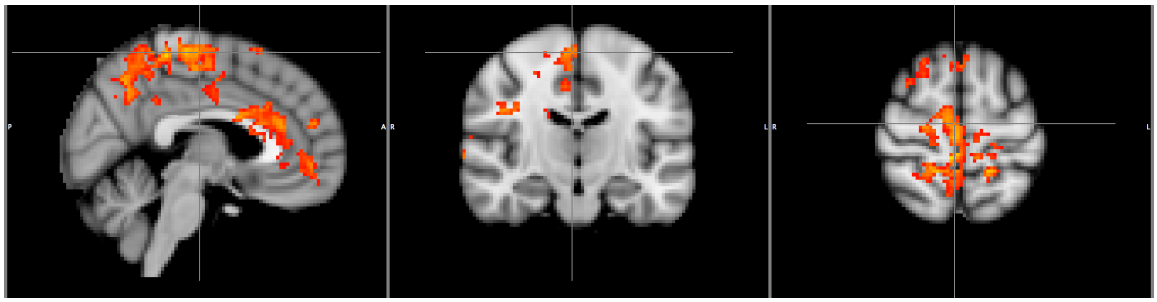


Figure 32. Partner group mean; Flame 1, Cluster 1.65, p <0.05, Premotor cortex.

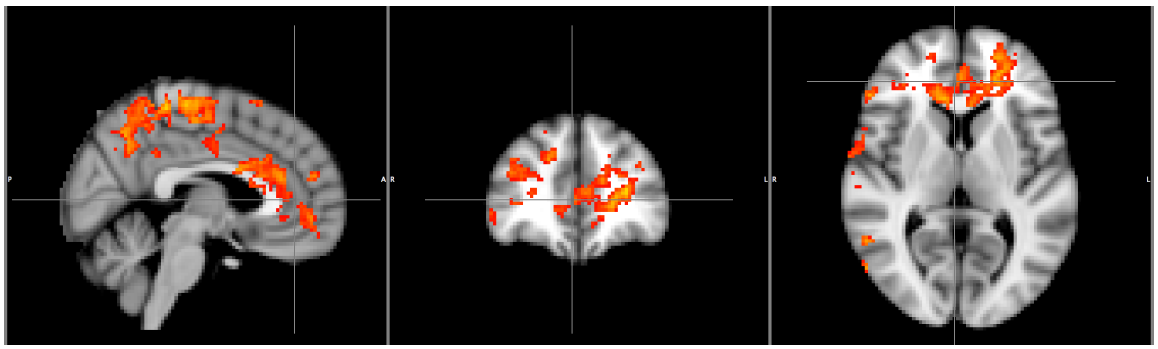


Figure 33. Partner group mean; Flame 1, Cluster 1.65, p <0.05, Prefrontal cortex

Additional results for self-stimulation and partner-induced stimulation orgasm combined group

Mid Stimulation > Early Stimulation

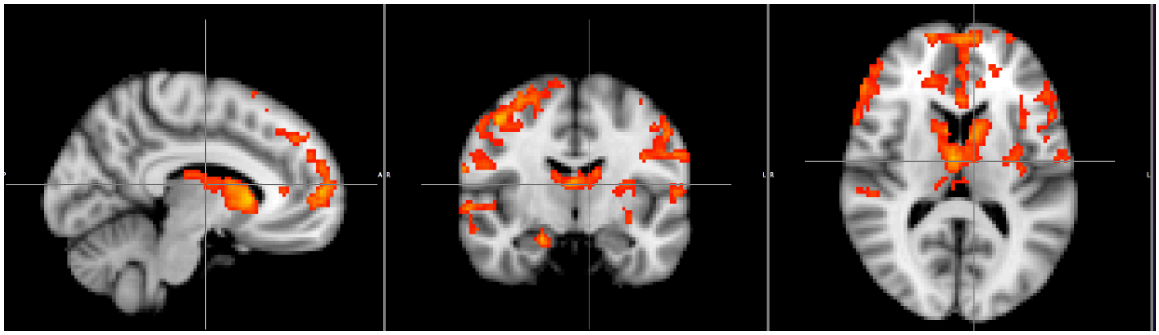


Figure 34. Thalamus activation: Mid stimulation > early stimulation. Flame 1, Cluster 1.65, p <0.05.

Orgasm > Early stimulation

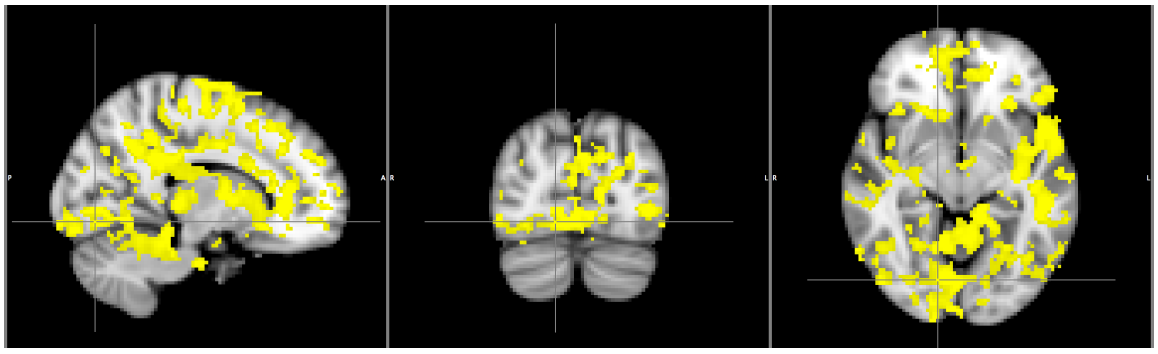


Figure 35. Visual cortex activations; Orgasm > early stimulation. Cluster z =2.0, p < .01.

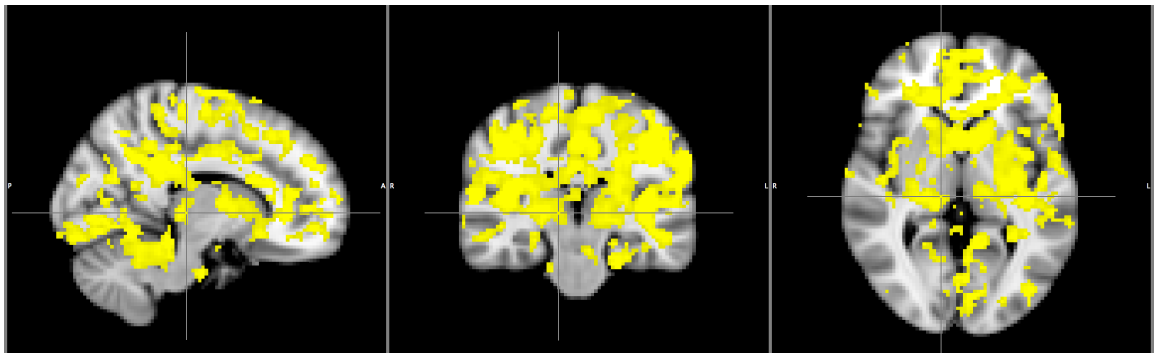


Figure 36. Bilateral thalamus activations: Orgasm > early stimulation Cluster z =2.0, p < .01.

Orgasm> Mid Stimulation

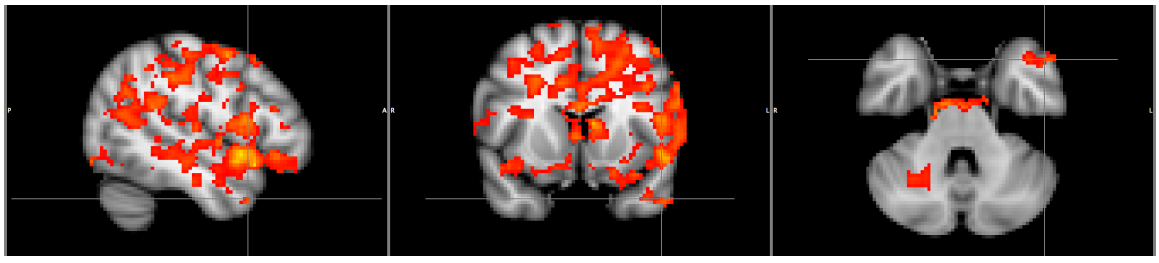


Figure 37. Left temporal pole activated at orgasm > mid stimulation. Flame 1, Cluster 1.65, p <0.05.

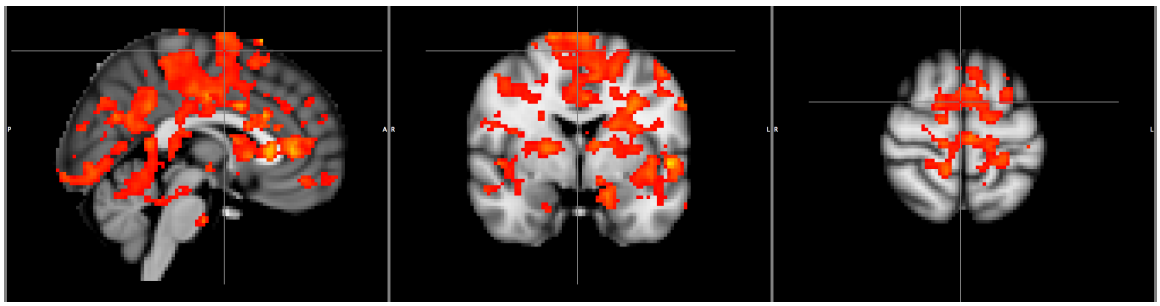


Figure 38. Supplementary Motor Area; Orgasm > mid stimulation. Flame 1, Cluster 1.65, p <0.05.

Orgasm> Late stimulation

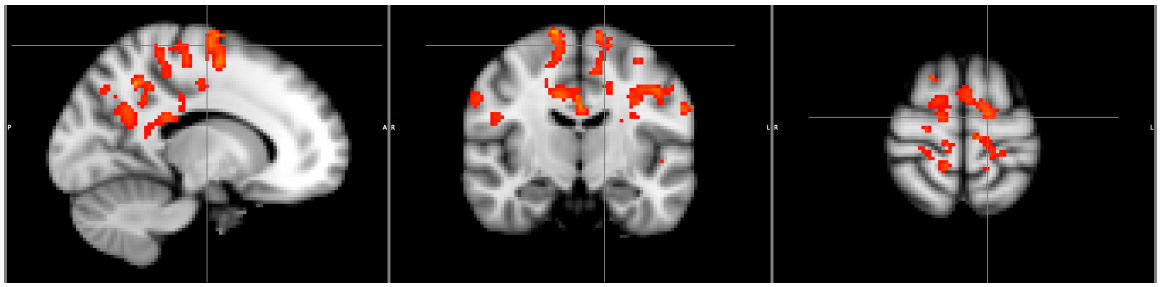


Figure 39. Premotor cortex activation: Orgasm > late stimulation. Flame 1, Cluster 1.65, p <0.05.

Orgasm> Early Recovery

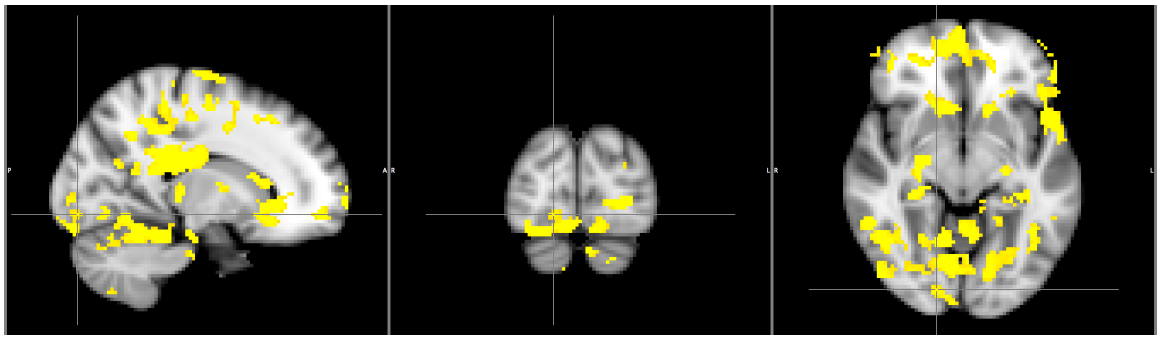


Figure 40. Visual cortex activation: Orgasm > early recovery. Flame 1, Cluster 1.65, p <0.05.

Appendix F. Debriefing Interview Results

Physical and cognitive cues for onset and offset of orgasm and recovery

Physical cues

Hair stands on edge—1
Muscles contracting--8
Skin tingling—3
Breathing speeds up -8
Racing heart—8
Heat—3
Sensations in genitals—3
Genital contractions—7
Breathholding—4
Moaning-3
Energy running through body-2
Spine arches—2
Pulse in throat—2
Skin hypersensitivity-1
Energy rushing out of genitals—1
Involuntary movements-2

Cognitive cues

Feeling like things are happening involuntarily –3
A sense of a locomotive approaching-1
Feeling things suspended—1
No thoughts in head—5
Feelings of letting go—3
A rush of hormones hitting the head—1
A splash of super-sweetness—1
A bright bursting expansive feeling in my head—1
A burning, yearning feeling of love

Orgasm ending

Physical sensations associated with orgasm ending

Muscles stop contracting—8
Breath slows down-7
Genital contractions stop—6
Waves of pleasure over—5
Body flush--3

Cognitive cues of orgasm ending

Conscious mind “kicked” back in-- 6
Sense of coming back to my senses—2
Could have continued, but felt you had enough data—consciously ended the orgasm—1

Recovery

Physical cues

Body settled down –2
Breathing back to normal—4
Muscles relaxed—6
No more buzzing sensations from genitals—2
Heart rate back to normal—4
Body feels heavy—4

Cognitive cues

Mind back all the way—5
Everything slowed down—2
Feel like I am coming back, like from yoga-1
Ready for another orgasm-1
Self-conscious of where I am –2
Feel complete and calm--2

Table 1. Orgasm estimate versus actual durations

Group	Orgasm Duration	Estimation	Difference
1 Self	12.6	2	10.6
2 Self	20.4	6	14.4
3 Self	58.6	45	13.6
4 Self	10.68	7	3.6
5 Self	14.96	8	6.9
6 Partner	38.61	27	11.6
7 Partner	49.04	40	9.04
8 Partner	25.74	10	15.7
9 Partner	55.34	8	47.3
10 Partner	50.74	11	39.7

Descriptive statistics for combined self and partner orgasm group

Variable	N	Range	Minimum	Maximum	Mean
Latency to orgasm	10	742.6	86.7	829.4	320.7
Orgasm duration	10	48.0	10.7	58.7	33.7
Recovery duration	10	66.7	22.5	89.2	51.0
Age	10	45.0	29.0	74.0	43.6
Movement (A) Absolute	10	2.5	.36	2.9	1.3
Movement (B) Relative	10	.17	.10	.27	.19
Arousal during stimulation	10	4.0	3.0	7.0	5.5
Fantasy during stimulation	10	1.0	.00	1.0	.7
	10	1.0	.00	1.0	.2
Orgasm intensity	10	3.0	4.00	7.0	5.35
Orgasm pleasure	10	4.0	3.00	7.0	5.35
Orgasm satisfaction	10	4.0	3.00	7.0	5.30
Ejaculation 0=no, 1=yes	10	1.0	.00	1.0	.10
Contractions 1=mild 2=moderate 3=strong	10	2.0	1.0	3.0	2.3
Breathholding 0=no, 1 =yes	10	1.0	.00	1.0	.40
Breath changes 1= speeds up 2=stops	10	1.0	1.0	2.0	1.40
Vocalization 0=no 1=yes	10	1.0	.00	1.00	.50
Orgasm estimate	10	43.0	2.0	45.	16.4

Appendix G.1. Women's clitoris, vagina, and cervix mapped on the sensory cortex: fMRI evidence.

Published in final edited form as:
J Sex Med. 2011 October ; 8(10): 2822–2830. doi:10.1111/j.1743-6109.2011.02388.x.

Women's clitoris, vagina and cervix mapped on the sensory cortex: fMRI evidence

Barry R. Komisaruk, PhD[1,2], **Nan Wise, LCSW**[1], **Eleni Frangos, BA**[1], **Wen-Ching Liu, PhD**[2,*], **Kachina Allen, PhD**[1], and **Stuart Brody, PhD**[3]

[1]Department of Psychology, Rutgers University, Newark, New Jersey

[2]Department of Radiology, New Jersey Medical School, University of Medicine and Dentistry of New Jersey, Newark, New Jersey

[3]School of Social Sciences, University of the West of Scotland, Paisley, United Kingdom

Abstract

Introduction—The projection of vagina, uterine cervix, and nipple to the sensory cortex in humans has not been reported.

Aims—To map the sensory cortical fields of the clitoris, vagina, cervix and nipple, toward an elucidation of the neural systems underlying sexual response.

Methods—Using functional Magnetic Resonance Imaging (fMRI) we mapped sensory cortical responses to clitoral, vaginal, cervical, and nipple self-stimulation. For points of reference on the homunculus, we also mapped responses to the thumb and great toe (hallux) stimulation.

Main Outcome Measures—fMRI of brain regions activated by the various sensory stimuli.

Results—Clitoral, vaginal, and cervical self-stimulation activate differentiable sensory cortical regions, all clustered in the medial cortex (medial paracentral lobule). Nipple self-stimulation activated the genital sensory cortex (as well as the thoracic) region of the homuncular map.

Conclusion—The genital sensory cortex, identified in the classical Penfield homunculus based on electrical stimulation of the brain only in men, was confirmed for the first time in the literature by the present study in women, applying clitoral, vaginal, and cervical self-stimulation, and observing their regional brain responses using fMRI. Vaginal, clitoral, and cervical regions of activation were differentiable, consistent with innervation by different afferent nerves and different behavioral correlates. Activation of the genital sensory cortex by nipple self-stimulation was unexpected, but suggests a neurological basis for women's reports of its erotogenic quality.

Introduction

The original map of the representation of the genitals in the sensory cortex in humans was generated by applying roving electrical stimulation to the brain in awake men, and asking the men from which part of their body the stimulation seemed to emanate. The men reported penile sensation when the interhemispheric region, i.e., the medial cortex (medial region of the paracentral lobule, Figure 1) was stimulated; they reported foot sensation when the electrical stimulation was applied immediately superior to the penile representation [1–3].

Corresponding Author: Barry Komisaruk brk@psychology.rutgers.edu, brk@andromeda.rutgers.edu.
*present address: Department of Radiology, OSF Saint Francis Medical Center, Peoria, IL 61637

Conflict of Interest:
None

While Penfield and Rasmussen [3] did not report the effect of brain stimulation on genital sensation in women, they did report that their patient with spontaneous sensory seizures likely stimulated by a small glioma in the postcentral gyrus near the falx (i.e., the interhemispheric component of the dura mater) had labial, breast, and foot sensations during her seizures.

Subsequent studies used electrical stimulation of the dorsal nerve of the penis to measure the distribution of evoked potentials in the cortex. Those studies confirmed the earlier homuncular map, for each reported that the evoked potentials were focused in the medial cortex, (in the medial region of the paracentral lobule), i.e., in the genital region as represented in the Penfield map [4–6]. Similar findings were reported by Allison et al [7] in response to electrical stimulation of the clitoris as well as the penis.

However, more recent studies using PET or fMRI, and another using penile evoked potentials, reported that a more dorsolateral portion of the paracentral lobule, rather than its medial region, was activated when direct penile stimulation was applied by the experimenter (using a toothbrush and recording fMRI [8]), when penile stimulation was applied by the subject's partner (using manual stimulation and recording PET [9]), or in response to electrical stimulation of the penis [10]. While the basis for this discrepancy in the penile map is still not reconciled, it is possible that sensory activation of the more dorsolateral region of the paracentral lobule may result from inadvertent and incidental stimulation of the groin, on the basis that Penfield's [3] map and even Kell's [8] "revised" map both show the transition zone between upper thigh and trunk (i.e., "groin") to be located on the dorsolateral region of the paracentral lobule.

A parallel discrepancy in the genital map of women has now become evident. Two recent studies, using fMRI with electrical stimulation of the clitoris [11] or using PET and mechanical stimulation of the clitoris by the subject's partner [12], reported that clitoral stimulation activated the dorsolateral, rather than the medial, region of the paracentral lobule. . In those studies, the clitoral stimulation was applied by the experimenter or the subject's partner.

As seen in the present findings, using fMRI, in which the women applied clitoral, vaginal or uterine cervical *self*-stimulation, there is clear evidence of activation of the medial region of the paracentral lobule, in the sensory genital region of the homuncular map of Penfield and Rasmussen [3]. In addition, there is an occasional secondary activation in the dorsolateral paracentral lobule, indicative of groin stimulation.

Rationale for the present research

The map of the genital sensory cortical representation is based almost exclusively on responses to penile and clitoral stimulation, both of whose afferent innervation is provided by the pudendal nerve. However, additional nerves convey sensation from the vagina and cervix, i.e., the pelvic, hypogastric and vagus nerves [13; for review: 14]. To our knowledge, the projection of vagina and uterine cervix to the sensory cortex in humans has not been reported previously. To address this gap, in the present study using fMRI, we mapped the regions of the sensory cortex that are activated by clitoral, vaginal, and cervical self-stimulation. For points of reference on the homunculus, we also mapped responses to the thumb and great toe (hallux) stimulation and nipple self-stimulation. Portions of these findings have been reported in abstract form [15].

Methods

Research Participants

Eleven healthy right-handed women, ages 23–56, recruited by word of mouth, were prescreened with the SCL-90 questionnaire to rule out any psychological contraindications to study participation. Each participant tested negative for pregnancy prior to scanning. All participants gave informed consent as required by the research protocol approved by the New Jersey Medical School – University of Medicine and Dentistry of New Jersey IRB. Participants were compensated $100 for participating in the study; the duration of each scan session was 1–2 hours.

Experimental Paradigm

A “boxcar” experimental design was employed with each 5-minute trial consisting of 30 sec of rest, then 30 sec of stimulation, repeated 5 times in succession. Control trials consisted of an experimenter rhythmically tapping a participant's thumb or toe in separate trials to establish reference points on the sensory cortex. Experimental mapping trials consisted of participants self-stimulating, by hand or personal device, using “comfortable” intensity, the clitoris, anterior wall of the vagina, the cervix, or the nipple, in separate, randomized-sequence trials. Clitoral self-stimulation was applied using rhythmical tapping with the right hand. Vaginal self-stimulation (of the anterior wall) was applied using the participant's own stimulator (typically a 15mm-diameter S-shaped acrylic rounded-top cylinder). Cervical self-stimulation was applied using a similar-diameter, glass or acrylic straight rounded-tip cylinder brought to the study by each participant. Nipple self-stimulation was applied using the right hand to tap the left nipple rhythmically. All trials started with a 30-sec rest period. The participants were instructed by an experimenter via headphones as to when to start and stop self-stimulation. The participants were in continuous audio contact with the experimenters for the duration of the experimental paradigm.

fMRI Acquisition

Data were collected using a 3T Siemens Allegra (head only) system using gradient-echo echo-planar sequence (EPIBOLD) with the following acquisition parameters: 2000/40 (TR/TE); 64X64 matrix, 22 cm field of view, 5-mm thick contiguous sections, and 90 degree flip angle. For each 5-min sensory paradigm, 150 image sets of 32 slices per TR were obtained using a standard quadrature “bird cage” head coil. The participant's head was stabilized with an individually-fitted thermoplastic frame that was affixed to the head coil to limit motion. Images were reconstructed from Siemens proprietary software (Advanced Neuropackage) and transferred to a remote workstation for processing and analysis.

Anatomical images

T1 weighted (TR/TE = 450/14, FOV=24 cm, Matrix=256x256, Slice thickness = 5 mm skip 0, 32 slices) high-resolution anatomical images were acquired in the transaxial plane in identical slice locations during each imaging session. This data set was used for image underlay with functional data to identify the anatomical landmarks.

Data analysis

Statistical parametric mapping (SPM-8) was utilized. In SPM-8, the blood-oxygenation-level-dependent (BOLD) signal intensity of each voxel during the stimulus conditions was compared statistically with its activity during the prestimulus condition (baseline condition). The images from each trial were pre-processed for realignment, normalized to MNI space, motion-corrected, and smoothed using an 8x8x10 kernel. The high pass filter was set to a default value of 128 sec to remove the slow signal drifts.

In order to obtain the overall presentation for each paradigm, group maps were generated with second level analysis using a random effects model. A canonical hemodynamic function was selected for the basis function to estimate the hemodynamics. To calculate the model parameters, the Restricted Maximum Likelihood (ReML) algorithm was used. In addition, an autoregressive model (AR) to correlate the time series was used with ReML to account for the aliased biorhythms and unmodeled neuronal activity.

MRIcro [32] was used for visualization of group maps on a standardized anatomical template. The numbers in the calibration bars in Figures 2 and 3c are the range of Z scores that correspond to the "hot metal" representation of the fMRI activity levels in the adjacent brain images. Thus, the closer the color of the brain activity is to "white hot", the more highly significant is that activity. Z scores: 1.96 = $p < 0.05$; 2.3 = $p<0.01$.

Results

Figure 2 shows the group maps of cortical responses to self-stimulation of clitoris, vagina, or cervix, or investigator-applied stimulation of left thumb or left hallux. The columns, (left to right: coronal, sagittal and transaxial views) show the maps of group data based upon Ns between 9 and 11. In these views, the convention is that the subjects' right side is on the left side of the image, as if their feet are closer to the observer than their head. For reference, in Figure 1, the homuncular map of Penfield and Rasmussen [3] is shown with lines indicating the relation between the boundaries of the postcentral gyrus laterally and the paracentral lobule medially on the schematic map and the brain anatomical template. As labeled in Figure 1, the paracentral lobule is the medial continuation of the more lateral postcentral (sensory) gyrus. In the Penfield and Rasmussen [3] homunculus, the face, hands and arms are represented in the postcentral gyrus, whereas the groin, legs, feet and genitals are located in the paracentral lobule. In Figure 2, the arrows indicate sensory cortical brain regions activated by the specific stimuli. Note that the response to stimulation of the thumb, in the postcentral gyrus, corresponded closely to the homuncular map. The group response to stimulation of the toe (weaker than that to the thumb) was in the medial region of the paracentral lobule, corresponding precisely to the homuncular map.

The group responses to clitoral, vaginal, and cervical self-stimulation were all located in the medial paracentral lobule, with the precise localizations being distinct from each other. Note that the groin region of the paracentral lobule (i.e., its dorsolateral region) was also activated in all but the thumb stimulation conditions. Note also the region of activation of the ventrolateral (sensory) thalamus by the clitoral self-stimulation condition. We have intentionally avoided "modeling out" the participants' hand movement involved in the self-stimulation. Note the absence of hand movement in the case of experimenter-applied thumb stimulation. Two unexpected observations were that a) although the participants were all using just their right hand to apply the self-stimulation, both the contralateral and ipsilateral hand areas were activated, a highly reliable effect, and b) in the case of investigator-applied toe stimulation, the participants' hand areas were also activated. These findings are addressed in the Discussion.

An unexpected finding was that nipple self-stimulation, which we had selected as a reference point on the homunculus, also activated the medial paracentral lobule, in the region activated by genital self-stimulation (Figure 3b and c).

A composite coronal view of the clitoral, vaginal and cervical activation sites is shown in Figure 3a. The sites are all in the medial paracentral lobule, but regionally differentiated. This clustered, but differential, localization pattern is likely due to the differential sensory innervation of these genital structures, i.e., clitoris: pudendal nerve, vagina: pelvic nerve,

and cervix: pelvic, hypogastric and vagus nerves (for review: [14]). It is likely that the overlap between the sites activated by vaginal and cervical self-stimulation (using a passive dildo) is due at least in part to the stretching stimulation of the vagina that inevitably accompanied the cervical self-stimulation.

The sagittal views in Figure 2 show that in each of the self-stimulation conditions, activation was evident also in the supplementary motor area, which is immediately rostral (anterior) to the paracentral lobule.

Figure 3b and c presents evidence that nipple self-stimulation activated not only, as expected, the thoracic (rib) region (as situated between the abdomen and the neck on the Penfield & Rasmussen homuncular map), but also, unexpectedly, the genital sensory cortex, i.e., the genital (medial) region of the paracentral lobule. Shown (Figure 3b) are superimposed responses to nipple and genital self-stimulation in three participants. Left panel: Note the overlap between activation produced by stimulation of nipple and cervix. Center panel: overlap between activation produced by stimulation of nipple, cervix and clitoris. Not unexpectedly, cervical self-stimulation activated the groin region of the dorsolateral paracentral lobule, probably as a consequence of unavoidable mechanical stimulation of the groin in the course of self-stimulating the cervix. Right panel: overlap among activation produced by stimulation of nipple, vagina, cervix and clitoris. Two unexpected observations were that nipple self-stimulation also activated the groin sensory region (dorsolateral paracentral lobule; Left panel) and, conversely, vaginal self-stimulation activated the thoracic nipple region (Center panel). Figure 3c is a three-axis view of the response to nipple self-stimulation in the brain shown in the center panel of Figure 3b.

Discussion

Clitoral, vaginal, and cervical self-stimulation differentially activated regions of the sensory cortex, but all were clustered in the medial paracentral lobule.

Because the perineal (groin) region is also stimulated incidentally during the clitoral, vaginal, and cervical self-stimulation, its corresponding sensory cortical region -- i. e, the dorsal convexity of the paracentral lobule, immediately lateral to the midline -- was also activated.

The present findings may help to resolve a discrepancy in the literature that claims that the location of the genital sensory cortical representation is on the dorsolateral paracentral lobule, rather than the medial paracentral lobule [8–12]. That is, based on the present findings, the discrepancy in the literature may be due to responses to indirect stimulation of the perineal (groin) region rather than to adequate stimulation of the genitals *per se*.

It is likely that the clitoris is indirectly stimulated by self-stimulation of the cervix or vagina. Under the conditions of the present study, it is not possible to discern whether the overlap among regions of the sensory cortex activated in response to self-stimulation of each of these three genital regions is due to true overlap of the brain regions that would be activated by “pure” stimulation of each of these three genital regions separately, or whether the overlap is due to incidental stimulation of one genital region (e.g., vagina) during self-stimulation of a different genital region (e.g., cervix). What is clear, however, is that to some extent, the sensory cortical regions activated by each of these three genital regions are to some extent separable and distinct. Unexpectedly, nipple/breast self-stimulation activated not only the (expected) thoracic sensory homuncular region, but also the region of the paracentral lobule that overlaps with the region activated by clitoral, vaginal, or cervical self-stimulation. This finding is consistent with many women's reports that nipple/breast stimulation is erotogenic and can elicit orgasms ([16–18] and personal communication).

The present finding of convergence between nipple and genital input in the genital sensory cortex is supported by an intriguing observation by Penfield and Rasmussen ([3], p.26): "One patient, Case E.D., a woman of 27 years who had a small glioma in the right postcentral gyrus next to the falx [i.e., the dura mater in the midline, separating the two cerebral hemispheres], experienced spontaneous sensory seizures that involved the left labium and left breast. At times…[the sensation] began in the left labium, spread to the left breast and continued to tingle in the labium and nipple. On one occasion this sensory aura was followed by twitching of the left foot…there was nothing in the sensation that resembled sexual excitement. But the description does suggest that the labium and nipple have a neighboring localization in the contralateral sensorimotor area near the motor representation for foot."

The ability of nipple stimulation to activate genital sensory cortex could have an indirect basis. Thus, nipple/breast self-stimulation-induced oxytocin secretion could stimulate uterine contractions that in turn generate afferent activity that projects to the paracentral lobule. However, it is also possible that nipple/breast and genital sensory activity converge directly not only on oxytocinergic neurons of the hypothalamic paraventricular nucleus [19], but also on paracentral lobule neurons of the genital sensory cortex.

The cerebellum activation observed in the present study during vaginal and cervical self-stimulation is a common observation during genital stimulation, especially during orgasm [12, 13]. It is likely that it is involved in controlling muscle tension during genital stimulation [14]. Two other brain regions that were seen to be activated in the present study are the supplementary motor area and SII (Secondary somatosensory cortex). Other brain regions activated more variably were thalamus, frontal and parietal cortices.

Regarding the observation of bilateral activation of the hand representation in sensory cortex in response to unilateral hand-applied self-stimulation that was noted in the Results section for clitoral and vaginal self-stimulation, it is likely that the sensory stimulation emanating from that single hand, by utilizing the corpus callosum, generates contra- as well as ipsi-lateral activation of the hand representation in sensory cortex. This observation is supported by substantial evidence in the literature of bilateral sensory cortical response to unilateral hand stimulation [20, 21]. A more curious observation was the activation of the hand representation in sensory cortex during investigator-applied toe stimulation. One speculation to account for this observation is that subtle muscle-induced contractions of the hand in response to toe stimulation (a compensatory response preparatory to breaking the fall in the "stumble" response: [22]) activates the hand representation area in the sensory cortex, although no obvious hand movement was observed. Another possibility is that the response is among the class of atypical forms of referred sensation (e.g., [23]).

The present findings provide evidence that, rather than vaginal stimulation being just an indirect means of stimulating the clitoris [17, 24], vaginal and cervical stimulation *per se* activate specific sensory cortical regions that are distinct from the clitoral sensory projection. These differential routes of entry into the brain are undoubtedly of significance in activating the diverse and differential consequences of clitoral, vaginal or cervical stimulation; they include differential physiological effects, e.g., on prolactin secretion [25], analgesia [26], and blood pressure reactivity to stress [27], and differential behavioral effects, e.g., on orgasm [28], sexual satisfaction [29], and intimate relationship quality [30, 31].

While the present study mapped the primary sensory field of genital input to the sensory cortex, it would be of interest in future studies to extend this analysis to brain fields beyond

the sensory cortex that are activated when genital stimulation is perceived as 'erotic' versus when it is perceived as 'just pressure'.

Acknowledgments

We are especially grateful to Dr. Robert Savoy for his generous provision of the head stabilization instrument. We thank Ms. Gladys Martinez for her insights and help, and gratefully acknowledge Ms. Sebina Versi, Ms. Sophie Greller and Ms. Grace Maher for their excellent technical assistance. Support: NIH 2 R 25 GM060826, the Rutgers University Research Fund, and The Carnegie Trust for the Universities of Scotland.

References

1. Foerster, O. Handbuch der Neurologie. Berlin: Springer; 1936. Sensible corticale Felder.
2. Penfield W, Boldrey E. Somatic motor and sensory representation in the cerebral cortex of man as studied by electrical stimulation. Brain. 1937; 60:389–443.
3. Penfield, W.; Rasmussen, T. The Cerebral Cortex of Man. New York: Macmillan; 1950.
4. Makela JP, Illman M, Jousmaki V, Numminen J, Lehecka M, Salenius S, Forss N, Hari R. Dorsal penile nerve stimulation elicits left-hemisphere dominant activation in the second somatosensory cortex. Hum Brain Map. 2003; 18:90–99.
5. Nakagawa H, Namima T, Aizawa M, Uchi K, Kaiho Y, Yoshikawa S, Orikasa S, Nakasato N. Somatosensory evoked magnetic fields elicited by dorsal penile, posterior tibial, and median nerve stimulation. Electroenceph Clin Neurophysiol. 1998; 108:57–61. [PubMed: 9474062]
6. Narici L, Modena I, Opsomer RJ, Pizzella V, Romani GL, Traversa R, Rossini PM. Neuromagnetic somatosensory homunculus: a non-invasive approach in humans. Neurosci Lett. 1991; 2:51–54. 121. [PubMed: 2020390]
7. Allison T, McCarthy G, Luby M, Puce A, Spencer D. Localization of functional regions of human mesial cortex by somatosensory evoked potential recording and by cortical stimulation. Electroenceph Clin Neurophysiol. 1996; 100:126–140. [PubMed: 8617151]
8. Kell CA, Kriegstein K, Rosller A, Kleinschmidt A, Lauf H. The sensory cortical representation of the human penis: revisiting somatotopy in the male homunculus. J Neurosci. 2005; 25:5984–5987. [PubMed: 15976087]
9. Georgiadis J, Holstege G. Human brain activation during sexual stimulation of the penis. J Comp Neurol. 2005; 493:33–38. [PubMed: 16255007]
10. Bradley WE, Farrell DF, Ojemann G. Human cerebrocortical potentials evoked by stimulation of the dorsal nerve of the penis. Somatosens Motor Res. 1998; 15:118–127.
11. Michels L, Mehnert U, Boy S, Schurch B, Kollias S. The somatosensory representation of the human clitoris: an fMRI study. Neuroimage. 2010; 49:177–184. [PubMed: 19631756]
12. Georgiadis J, Kortekaas R, Kulpers R, Nieuwenburg A, Pruim H, Reinders S, Holstege G. Regional cerebral blood flow changes associated with clitorally induced orgasm in healthy women. Eur J Neurosci. 2006; 24:3305–3316. [PubMed: 17156391]
13. Komisaruk BR, Whipple B, Crawford A, Grimes S, Liu W-C, Kalnin A, Mosier K. Brain activation during vaginocervical self-stimulation and orgasm in women with complete spinal cord injury: fMRI evidence of mediation by the Vagus nerves. Brain Res. 2004; 1024:77–88. [PubMed: 15451368]
14. Komisaruk, BR.; Beyer, C.; Whipple, B. The Science of Orgasm. Baltimore: The Johns Hopkins University Press; 2006. p. 358
15. Komisaruk BR, Wise N, Frangos E, Liu W. Women's clitoris, vagina and cervix mapped on the sensory cortex, using fMRI. Soc Neurosci. 2009 562.18, October.
16. Kinsey, A.; Pomeroy, W.; Martin, C.; Gebhard, P. Sexual Behavior in the Human Female. Philadelphia: WB Saunders; 1953.
17. Masters, W.; Johnson, V. Human Sexual Inadequacy. Boston: Little, Brown; 1970.
18. Paget, L. The Big O. New York: Broadway Books; 2001.
19. Netter, FH. Anatomy and Physiology. Summit, NJ: Ciba Pharmaceutical; 1986. The Ciba Collection of Medical Illustrations. Nervous System. Part I.

20. Blatow M, Nennig E, Durst A, Sartor K, Stippich C. FMRI reflects functional connectivity of human somatosensory cortex. Neuroimage. 2007; 37:927–936. [PubMed: 17629500]
21. Sutherland MT. The hand and the ipsilateral primary somatosensory cortex. J Neurosci. 2006; 26:8217–8218. [PubMed: 16906643]
22. Haridas C, Zehr EP. Coordinated interlimb compensatory responses to electrical stimulation of cutaneous nerves in the hand and foot during walking. J Neurophysiol. 2003; 90:2850–2861. [PubMed: 12853441]
23. Richter C. Mysterious form of referred sensation in man. Proc Natl Acad Sci USA. 1977; 74:4702–4705. [PubMed: 270709]
24. O'Connell HE, Eizenberg N, Rahman M, Cleeve J. The anatomy of the distal vagina; towards unity. J Sex Med. 2008; 5:1883–1891. [PubMed: 18564153]
25. Brody S, Kruger THC. The post-orgasmic prolactin increase following intercourse is greater than following masturbation and suggests greater satiety. Biol Psychol. 2006; 71:312–315. [PubMed: 16095799]
26. Whipple B, Komisaruk BR. Analgesia produced in women by genital self-stimulation. J Sex Research. 1988; 24:130–140.
27. Brody S. Blood pressure reactivity to stress is better for people who recently had penile-vaginal intercourse than for people who had other or no sexual activity. Biol Psychol. 2006; 71:214–222. [PubMed: 15961213]
28. Cutler WB, Zacker M, McCoy N, Genoves-Stone E, Friedman E. Sexual response in women. Obstet Gynecol. 2000; 95(4,suppl 1):S19.
29. Tao P, Brody S. Sexual behavior predictors of satisfaction in a Chinese sample. J Sex Med. 2011; 8:455–460. [PubMed: 21114768]
30. Costa RM, Brody S. Women's relationship quality is associated with specifically penile-vaginal intercourse orgasm and frequency. J Sex Marital Ther. 2007; 33:319–327. [PubMed: 17541850]
31. Brody S. The relative health benefits of different sexual activities. J Sex Med. 2010; 7:1336–1361. [PubMed: 20088868]
32. Rorden C, Brett M. Stereotaxic display of brain lesions. Behav Neurol. 2000; 12:191–200. See also http://www.cabiatl.com/mricro/mricro/index.html. [PubMed: 11568431]

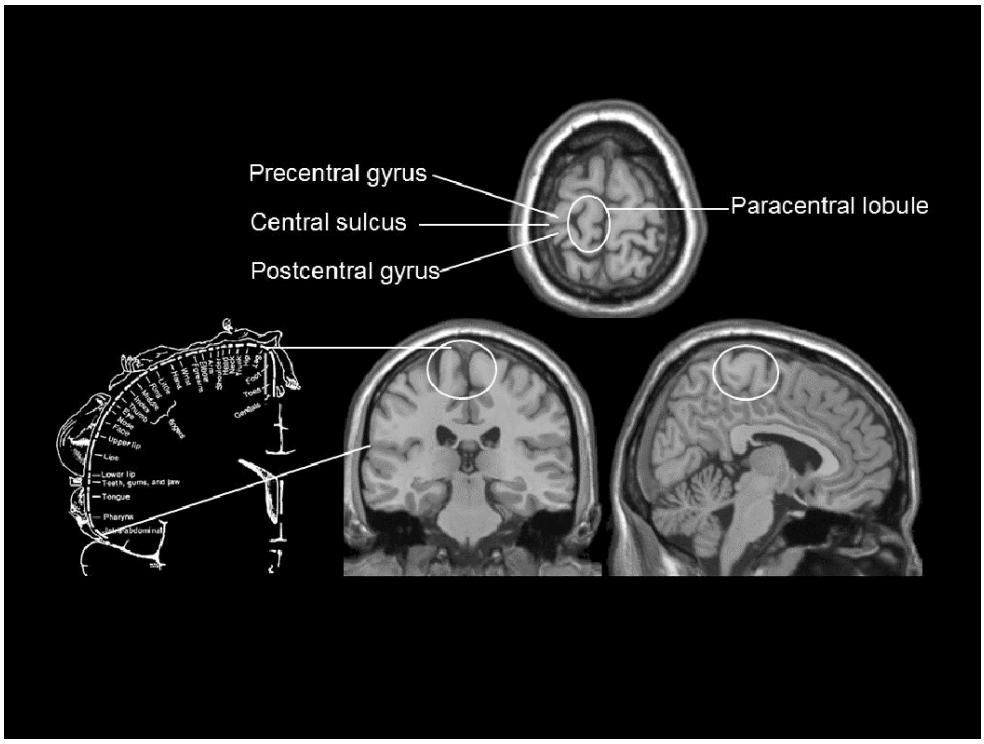


Figure 1.
Three views of the paracentral lobule, showing its relation to adjacent cortical regions (adapted from [32]). The relation of the paracentral lobule to the sensory cortical homunculus of Penfield and Rasmussen [3] is shown by the lines connecting the corresponding regions.

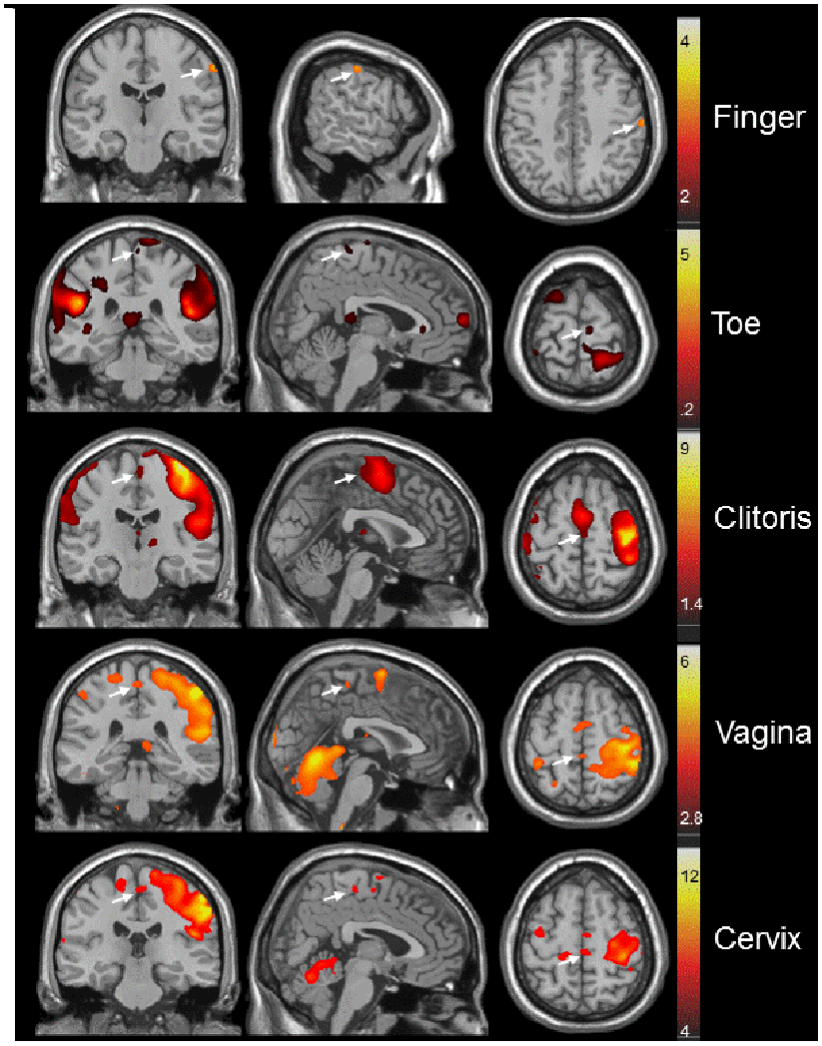


Figure 2.
Three-axis (columns: coronal, sagittal and transaxial) views of the group-based responses to experimenter-applied (finger and toe) or participant self-applied (clitoris, vagina, or cervix) stimulation in relation to the homuncular map (adapted) generated by Penfield and Rasmussen [3]. The arrows indicate the sensory cortical regions activated by the various stimulated body regions. Finger stimulation activated the postcentral (sensory) gyrus. Hallux (large toe) stimulation activated the medial paracentral lobule. Clitoral, vaginal, cervical, and nipple self-stimulation also activated the medial paracentral lobule. Note that the perineal (groin) region just lateral to the midline in the paracentral lobule was also activated by clitoral, vaginal, and cervical self-stimulation. There was marked hand-related activation

in the postcentral gyrus, and continuation of activation into the supplementary motor area immediately rostral to the sensory cortical responses, in the self-stimulation conditions. The secondary sensory cortex (SII; at the base of the homunculus) was activated under all the stimulus conditions (not evident in these images in the thumb stimulation condition). The "hot-metal" calibrations show the range of Z-scores for the intensity of the fMRI responses.

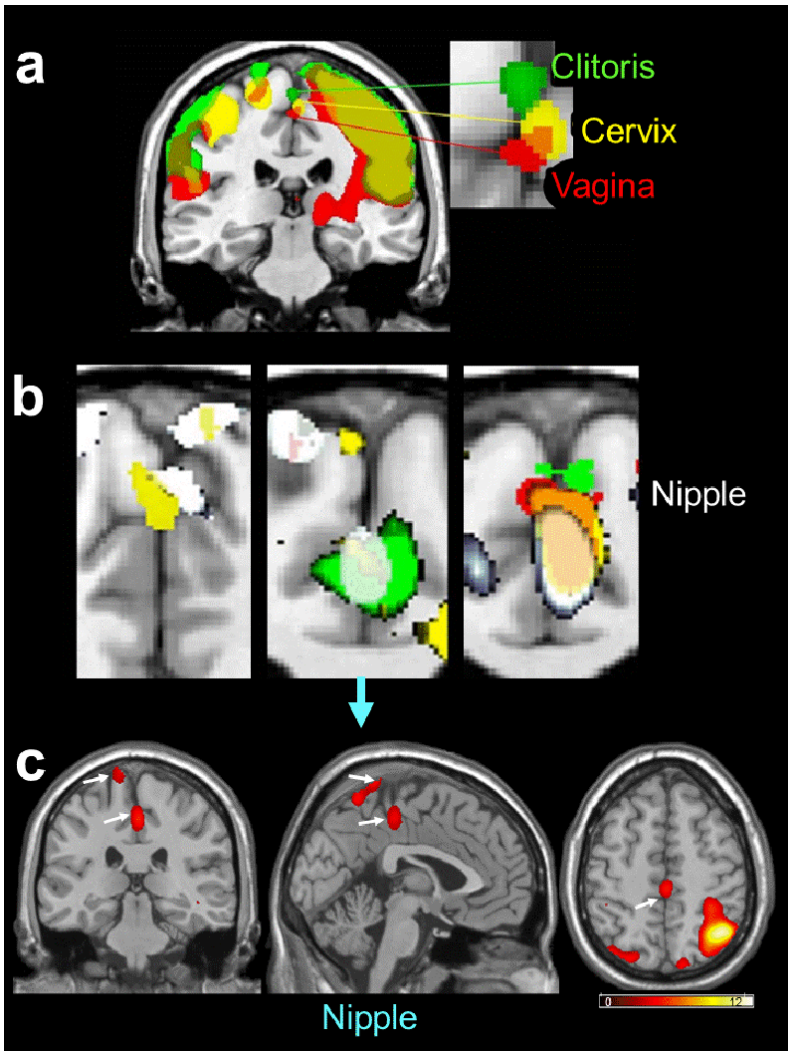


Figure 3.
a: Group-based composite view of the clitoral, vaginal and cervical activation sites, all in the medial paracentral lobule, but regionally differentiated. We interpret this as due to the differential sensory innervation of these genital structures, i.e., clitoris: pudendal nerve, vagina: pelvic nerve, and cervix: hypogastric and vagus nerves (e.g., [14]).
b: Nipple self-stimulation activated not only the thoracic region, but also unexpectedly, the genital region of the medial paracentral lobule. Shown are superimposed responses to nipple and genital self-stimulation in three participants. Note the congruence between activation produced by stimulation of nipple and cervix (left panel), nipple, cervix and clitoris (center panel), and nipple, vagina, cervix and clitoris (right panel). Not unexpectedly, cervical self-

stimulation activated the groin region (center panel). However, it is surprising that vaginal self-stimulation activated the thoracic nipple region (center panel), and nipple self-stimulation activated the groin sensory region (left panel). Color coding: nipple (white), cervix (yellow), clitoris (green), vagina (red, or when congruent with nipple - pink).
c: Three-axis view of the response to the nipple self-stimulation in the case of the center image of Figure 3(b) (downward pointing blue arrow).

Appendix G.2.1. Effective connectivity among brain components during the orgasm sequence in humans

Print this Page

NEUROSCIENCE 2012

Presentation Abstract

Program#/Poster#: 676.07/II17

Presentation Title: Effective connectivity among brain components during the orgasm sequence in humans

Location: Hall F-J

Presentation time: Tuesday, Oct 16, 2012, 3:00 PM - 4:00 PM

Authors: ***N. J. WISE**, J. DELL'ITALIA, C. FINNERTY, K. ALLEN, E. FRANGOS, B. R. KOMISARUK;
Psychology, Rutgers Univ., Newark, NJ

Abstract: Background: Starting with genital stimulation, what is the chain of activation of brain components leading up to, during, and after orgasm? We previously reported that in the orgasm process, using fMRI, specific brain components became activated by genital self-stimulation in differential temporal sequence (Komisaruk et al, 2010, SFN abst 285.6). However, knowledge of that sequence does not inform as to which brain component activates the next brain component in the sequence. Question: What are the patterns of connectivity among specific brain components activated during orgasm, and (how) does the connectivity change over the course of the orgasm sequence? Method: Graphical causal modeling analysis was used to measure effective connectivity between paracentral lobule, cerebellum, frontal pole and nucleus accumbens in males and females. These regions were chosen based on their activation in previous General Linear Model analyses. The orgasm sequence was divided into 3 parts for purpose of analysis: buildup to orgasm, orgasm, and post-orgasm. Results (preliminary): A commonality among individuals included distinctly different patterns in the transitions from buildup to orgasm to the post-orgasm phase. During buildup, a commonality among individuals was that activity in the paracentral lobule, cerebellum and nucleus accumbens “fed-forward”, converging on the frontal pole. During the post-orgasm phase, we observed a negative feed-forward, suggesting inhibition, from nucleus accumbens to paracentral lobule among individuals. The connectivity pattern changed markedly during orgasm, characterized

by varying degrees of convergence and divergence related to individual and/or sex differences. As one example, activity from paracentral lobule fed-forward, diverging to all three regions -- frontal pole, cerebellum and nucleus accumbens -- and they, in turn, converged back to paracentral lobule, suggesting a reciprocal connection. Conclusion: This study constitutes the first effective connectivity analysis of human orgasm. While we recognize the limitations of the present approach, e.g., a few selected regions of interest (ROIs) and limited sample size, nevertheless, we observed significant connectivity patterns and changes among them related to the orgasm sequence. Further exploration using this analytical approach should help elucidate how specific connectivity patterns among brain components contribute to the behavioral, cognitive, and affective components of orgasm.

Disclosures: **N.J. Wise:** None. **J. Dell'Italia:** None. **C. Finnerty:** None. **K. Allen:** None. **E. Frangos:** None. **B.R. Komisaruk:** None.

Keyword(s): SEXUAL BEHAVIOR

FUNCTIONAL MRI

FUNCTIONAL CONNECTIVITY

Support: RUBIC

Rutgers University Foundation

NIH-NIGMS 2R25 GM060826

[Authors]. [Abstract Title]. Program No. XXX.XX. 2012 Neuroscience Meeting Planner. New Orleans, LA: Society for Neuroscience, 2012. Online.

Effective connectivity among brain components during the orgasm sequence in humans

N. J. WISE , K. ALLEN, C. FINNERTY, E. FRANGOS, J. DELL'ITALIA, B. R. KOMISARUK

Department of Psychology, Rutgers University, Newark, NJ 07102

676.07 / II17

Introduction

• Orgasm involves the buildup of excitation of neural elements over a period of minutes, a peak of activity, and then a subsidence following the orgasm.

• Our previous studies showed differential sequence of activations of different brain regions leading up to orgasm, with the peak involving widespread activation, followed by a substantial reduction in activity (Komisaruk et al., 2010, 2011a).

• Conventional fMRI data analyses do not reveal brain network dynamics. The present study applies a recently developed method (IMaGES) of "effective connectivity" which ascertains patterns of temporal characteristics among selected brain regions.

• Based on our previous findings, we selected 4 brain regions of interest (ROIs) that are reliably activated during orgasm, and analyzed their effective connectivity during the build-up to orgasm, orgasm, and post- orgasm.

• Three types of orgasm induction were analyzed: penile self-stimulation, clitoral self-stimulation, and thought-induced orgasm (without physical stimulation) in women.

To our knowledge, this is the first analysis of effective connectivity in the orchestration of regions involved in the brain "symphony" of orgasm.

Background

Genital Sensory Cortex

• Clitoral, vaginal, and cervical self-stimulation activate specific, different regions of the sensory cortex, all clustered in the mesial paracentral lobule in the Paracentral Cortex, (Komisaruk et al., 2011 b).

"Thought-induced" activation of the genital sensory cortex

• Our previous study showed that *thinking* about clitoral stimulation activates genital somatosensory cortex (Wise et. al., 2011) overlapping the homuncular region activated by *physical* stimulation of the clitoris (Komisaruk et al., 2011b).

"Thought-induced" orgasm

• Thought-induced orgasm was reported to result in physiological changes comparable to that of orgasm induced by genital stimulation (Whipple, Ogden & Komisaruk, 1992)

• To our knowledge, there are no published studies of brain activity correlated with thought-induced orgasm.

Brain studies of orgasm: discrepancy

• In contrast to our reports based on fMRI of activation of frontal cortex stimulation-induced orgasm, analysis of partner-induced orgasm using Emission Tomography (PET) reported significant frontal region deactivation (Georgiadis et. al., 2009).

Methods

Selection of ROIs

Based on our previous time-course analysis, we selected 4 ROIs involved in sensory (Paracentral), motor (Cerebellar Tonsil), cognitive (Frontal Pole), and reward (Nucleus Accumbens).

Research Participants

Twelve healthy women (ages 23-56) and 5 healthy men (ages 28-71) participated in the present study, which was approved by the Rutgers University IRB.

Groups:

1. Clitoral self stimulation orgasm: 8 women (n= 9 orgasms)
2. Penile stimulation orgasm: 5 men (n= 5 orgasms)
3. Thought-induced orgasm : 4 women (n= 4 orgasms)

Experimental Paradigm

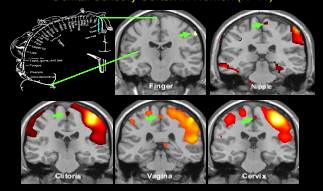
The participants self-stimulated to orgasm, either genitally, or by thought without physical stimulation. The start and end of orgasm was indicated by button press or hand raise.

fMRI acquisition

Data were collected using a 3T Siemens Allegra and 3T Siemens Trio. Individuals were scanned in the transaxial plane using standard functional MR imaging BOLD and high-resolution MPRAGE anatomical protocols. The orgasm sequence conditions were defined as follows:

1. "Start" included 1 TR before stimulation began plus 8 TRs forward.
2. "Pre-orgasm" included 1 TR after orgasm began plus 8 TRs backward.
3. "Orgasm" included 1 TR before orgasm began plus 8 TRs forward.
4. "Post-Orgasm" included 1 TR before the end of orgasm plus 8 TRs forward.

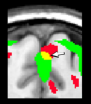
Genital Sensory Cortex in Women (N=11)



Note that self-stimulation of the clitoris, vagina, cervix and nipple resulted in activations in the mesial paracentral lobule.

Clitoris

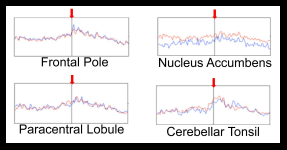
think/tap/overlap



N = 9
N = 11

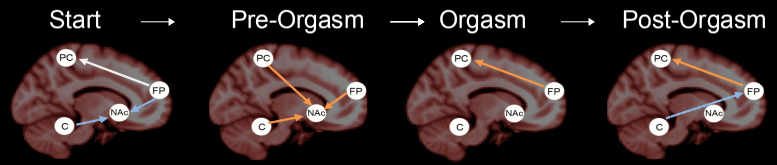
"Thinking" of stimulation of a body part and physical stimulation of that body part activated overlapping regions of the somatosensory cortex, specifically the paracentral lobule.

Time Course of ROIs



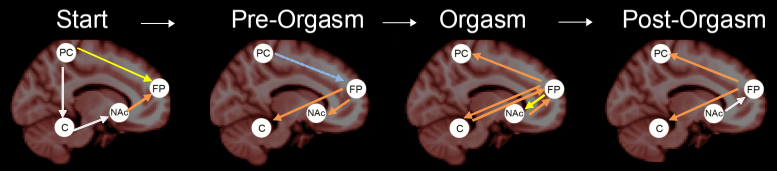
The time course activity of the selected ROIs: two minutes before orgasm (at orgasm (red arrow) and two minutes after.

Male Orgasm, Penis Self Stimulation



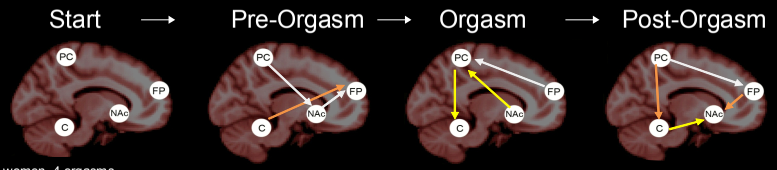
5 men, 5 orgasms

Female Orgasm, Clitoral Self Stimulation



8 women, 9 orgasms

Female Orgasm, Thought-Induced



4 women, 4 orgasms

P< .01
P< .05
P< 1 (trend)
Non-significant connection

Methods continued:

Preprocessing

fMRI data for the task were registered into MNI standard space using FSL (FMRIB's Software Library). Motion correction was performed using the MCFLIRT module in FSL and brain extraction was performed using BET. Region of interest (ROI) masks were created using the Harvard-Oxford Cortical and Subcortical Structural Atlas, and average time series for these ROIs were extracted using the FSL mean TS module. Time series were compiled into matrices for each individual subject for all ROIs, and matrices for the subjects in each group were used as input into the IMaGES module in the program Tetrad.

IMaGES (Independent Multi-sample Greedy Equivalence Search)

The methods we use are adapted from the Greedy Equivalence Search (GES) (Meek 1997). The search procedure begins with an empty graph with no presumed connections between nodes and edges, and proceeds to search forward, one new connection at a time. The algorithm searches for the best fitting models (defined as acyclic graphs meeting the conditional independence assumptions of a Markov Equivalence class), which are scored using the Bayesian Information Criterion (BIC) (Schwarz, 1978). The BIC is calculated using the maximum likelihood estimate of the model's free parameters plus the dimension of the model (in our case, the number of connections plus the number of brain regions) taking into account the sample size. The algorithm searches forward from the empty graph until no improvement in BIC score is possible, and then backwards, and outputs a description of the best fitting models. In practice, the algorithm requires a computation of a series of maximum likelihood estimates, and is limited to cases where approximations to such estimates can be obtained rapidly. These models may be parameterized and tested in conventional ways.

Results

• Each group showed sequential changes in the connectivity among the ROIs leading up to, during, and after orgasm, and these patterns differed among the 3 groups.

• We observed a significant projection from Frontal Pole to Paracentral Cortex (genital sensory cortex) during orgasm in all 3 groups.

• Gender differences were evident in the brain activity patterns.

• During "thought-induced" pre-orgasm and post-orgasm sequences, there was significant output from the Paracentral Cortex to other ROIs. This supports our previous evidence that thinking of genital stimulation without physical stimulation activates the genital sensory cortex.

• In the clitoral self-stimulation "orgasm" condition, there were reciprocal relationships between Frontal Pole and Nucleus Accumbens, as well as Frontal Pole and Cerebellum.

Conclusions

• We recognize the main limitations of the present study -- specifically, the limited number of participants, and the brief duration of orgasm, which places constraints on the optimal number of TRs per condition for the IMaGES analysis.

• While our previous time course analysis of orgasm showed sequential patterns of ROI activation, the present study directly examines predictive relationships (effective connectivity) before, during, and after orgasm.

• The present study provides evidence that interactions among brain regions associated with cognitive (Frontal Pole), sensory (Paracentral Cortex), affective (Nucleus Accumbens) and motor (Cerebellar Tonsil) processes change sequentially leading up to, during, and after orgasm.

• The unique type of data analysis provided by IMaGES raises the intriguing question of the difference in cognition that may be generated, e.g., during afference to the Frontal Cortex versus efference from the Frontal Cortex.

References

Georgiadis, J. Reinders, A., Paans, A., Renken, R. & Kortekaas, R. (2009). Men versus women on sexual brain function: prominent differences during tactile genital stimulation, but not during orgasm. *Human Brain Mapping, 30*, 3089-3101.

Komisaruk, B.R., Wise, N., Frangos, E., & Allen, K. (2010) An fMRI time-course analysis of brain regions activated during self-stimulation to orgasm in women. Program No. 285.6. 2010. Neuroscience Meeting Planner. San Diego CA: Society for Neuroscience, 2010. Online

Komisaruk, B. R., Wise, N., Frangos, E., Barbano, W., & Allen, K. (2011a). . An fMRI video animation time-course analysis of brain regions activated during self-stimulation to orgasm in women. Neuroscience Meeting Planner. Washington D.C.: Society for Neuroscience, 2011. Online

Komisaruk, B.R., Wise, N., Frangos, E., Liu, W.C., Allen, K., & Brody, S. (2011b) Women's Clitoris, Vagina, and Cervix Mapped on the Sensory Cortex: fMRI evidence. *Journal of Sexual Medicine*, 8(10), 2822-2830.

Meek, C. (1997). Graphical Models: Selecting causal and statistical models. PhD thesis, Carnegie Mellon University.

Ramsey, J. D., Hanson, S. J., Hanson, C., Halchenko, Y. O., Poldrack, R. A. & Glymour, C. (2011). Six problems for causal inference from fMRI. *NeuroImage*, 49(2) 1545-58.

Ramsey, J. D., Hanson, S.J., & Glymour, C. (2011). Neuroimage (multi-subject search correctly identifies causal connections and most causal directions in the DCM models of the Smith et al. simulation. *NeuroImage*, 58(3), 838-848.

Schwarz, G. (1978) Estimating the dimension of a model. *Ann. Stat.* 6, 461–464.

Whipple, B., Ogden, G., & Komisaruk, B. R. (1992). Physiological correlates of imagery-induced orgasm in women. *Archives of Sexual Behavior*, 21 (2) 121-133.

Wise, N., Frangos, E., & Komisaruk, B.R. (2010). Tactile imagery somatopically activates genital sensory homunculus: fMRI evidence. Program No. 80108. 2010. Neuroscience Meeting Planner. San Diego, CA: Society for Neuroscience, 2010. Online

Acknowledgments

Funded by a grant from Rutgers University Brain Imaging Center (RUBIC), (NW).
Special thanks to Wendy Brittano and Radhun Tellor for excellent technical assistance.

Appendix G.2.2. Men's genital structures mapped on the sensory cortex: fMRI evidence.

Print this Page

Neuroscience 2013

Presentation Abstract

Program#/Poster#:	464.04/AAA22
Presentation Title:	Men's genital structures mapped on the sensory cortex: fMRI evidence
Location:	Halls B-H
Presentation time:	Monday, Nov 11, 2013, 4:00 PM - 5:00 PM
Topic:	++D.09.d. Functional organization
Authors:	***B. R. KOMISARUK**, K. ALLEN, N. WISE, E. FRANGOS, W. BIRBANO; Dept Psychology, Rutgers, The State Univ. of New Jersey, NEWARK, NJ
Abstract:	Men's genitals are innervated by at least three pairs of nerves - pudendal, pelvic, and hypogastric. The same named three pairs of nerves in women provide sensory innervation of the clitoris, vagina/cervix, and uterus, respectively. Using fMRI, we previously reported that self-stimulation of these genital regions in women activates different, but partially overlapping, regions of the paracentral lobule (PCL) of the primary sensory cortex, as does nipple self-stimulation (J Sex Med 2011; 8: 2822). A comparable mapping of penile glans and shaft, scrotum, testicles, urethra, and nipples has not been reported in men. In the present study we analyzed the brain regions activated by mild and forceful self-stimulation of penile glans, penile shaft, scrotum, testicles, and nipples. Preliminary results: Self-stimulation of specific genital structures activated differentially distributed regions of the PCL of the primary sensory cortex, in addition to secondary sensory cortex, insula, anterior cingulate and frontal cortices, thalamus and cerebellum. Mild self-stimulation of penile glans or shaft activated a region of PCL inferior to that activated by forceful compression of the same structures. Self-stimulation of testicles activated a region of the PCL deeper (i.e., farther from the surface) than did stimulation of the other genital structures. Nipple self-stimulation activation overlapped the PCL regions that were activated by genital stimulation, as we reported previously in women. These findings provide evidence that the differential regional activation of PCL to self-stimulation of specific genital structures in men is related to their differential innervation. Knowledge of the regional primary sensory cortical responses to the specific components of the genital

system in men is of potential significance in the understanding and treatment of sexual dysfunction.

Disclosures: **B.R. Komisaruk:** None. **K. Allen:** None. **N. Wise:** None. **E. Frangos:** None. **W. Birbano:** None.

Keyword(s): SEX

NEUROIMAGING

HUMAN

Support: NIH-NIGMS NIH 5 R 25 GM 096161-02

Rutgers University RUBIC

Men's genital structures mapped on the sensory cortex: fMRI evidence 464.04

Barry R. Komisaruk, Kachina Allen, Nan Wise, Eleni Frangos, and Wendy Birbano
Department of Psychology, Rutgers University, Newark, NJ 07102

Introduction

Men's genitals are innervated by at least three pairs of nerves – pudendal, pelvic, and hypogastric (see Figure) [1]. The same three pairs of nerves in women provide sensory innervation of the clitoris, vagina/ cervix, and uterus, respectively.

Using fMRI, we previously reported that self-stimulation of these genital regions in women activates different, but partially overlapping, regions of the paracentral lobule of the sensory cortex, as does nipple self-stimulation [2]. To our knowledge, a comparable comprehensive mapping of the genital structures in men has not been reported.

Previous work on genital mapping in men included a report of responses to rectal stimulation; however, it did not include activation in the somatosensory cortex [3]. Electrical stimulation of the dorsal nerve of the penis confirmed the earlier homuncular map of Penfield [4], i.e., that the evoked potentials were focused in the medial cortex (in the medial region of the paracentral lobule), i.e., in the genital region as represented in the homuncular map [5–8]. Other studies using mechanical or electrical stimulation of the penis identified a responsive region that was either medial [9] or more dorsolateral [10-12]; however, the latter may have been due to inadvertent stimulation of the groin. It is likely that, as in women [2], the different nerves providing sensory innervation of the genitals in men project to distinctly different regions of the sensory cortex.

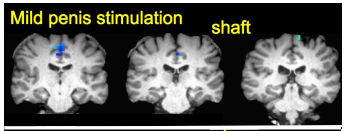
To identify where the afferents from different genital components in men project onto the sensory cortex, we analyzed the localization of activation sites in sensory cortex in response to self-stimulation of the penile glans and shaft, scrotum, testicles, urethra, perineum, rectum, prostate and nipples.

Sensory Nerve	Genital Region	
	Female	Male
Pudendal	clitoris + labia + perineum	penile skin + scrotum + perineum
Pelvic	vagina + cervix	penile deep + urethra + rectum ?
Hypogastric	cervix + uterus	testicles + prostate
Vague (?)	vagina + cervix + uterus?	prostate?

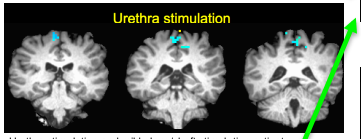
Methods

While lying in a 3T Siemens Trio scanner subjects were given visual cues to self stimulate each area of interest typically for 30sec+30sec rest x 5. Each subject used his right hand to stimulate his nipples, testicles and penis and a disposable curved lucite rod to stimulate his prostate, rectum and perineum. The urethra was stimulated using a thin (#8) commercial sterile catheter. Data processing was carried out in FSL and AFNI in Talairach space. The hand movements required for stimulation were modeled and subtracted from stimulation activations to ensure that stimulation activations were independent of the movements required to perform the stimulation. An ROI analysis was carried out on the paracentral lobules (AFNI TTAtlas) and thresholds were adjusted to see only the most active voxels.

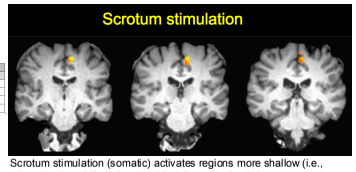
Numbers of participants for the data figures:
Shaft comparison deep versus mild, shaft, glans, scrotum, testicles, n=10
Nipple, left/right, n=5
Urethra, prostate, rectum, prostate-rectum:, n=4,



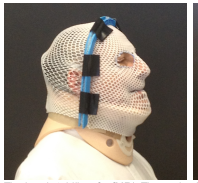
Contrast the superficial stimulation here with deep stimulation



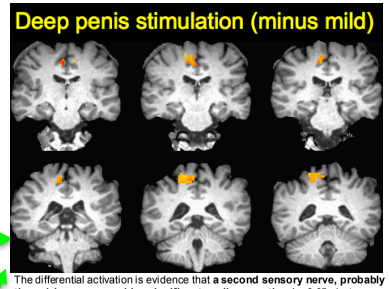
Urethra stimulation and mild glans/shaft stimulation activate regions different from those activated by deep penis stimulation



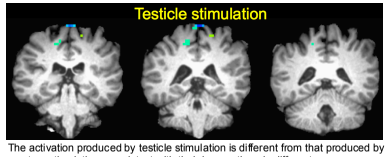
Scrotum stimulation (somatic) activates regions more shallow (i.e., (closer to the midline) than testicle (visceral) stimulation


The head stabilizer for fMRI. The neck brace is fitted first (note extension up to occipital region), followed by the thermoplastic mesh molded to back of the head, then to the face.

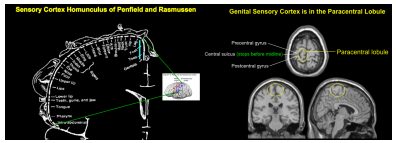

Prostate-rectum-perineum self-stimulator. Disposable, single use. Lubricated with petroleum jelly.

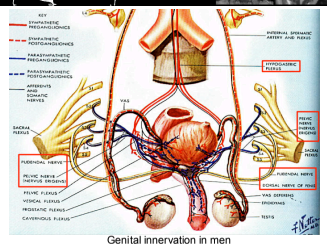


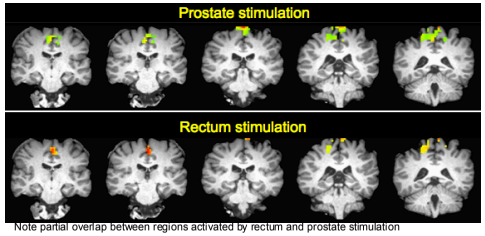
The differential activation is evidence that **a second sensory nerve, probably the pelvic nerve, provides significant penile sensation** ($p<0.05$ cluster thresholded)



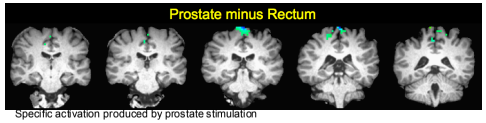
The activation produced by testicle stimulation is different from that produced by scrotum stimulation, consistent with their innervation via different nerves.



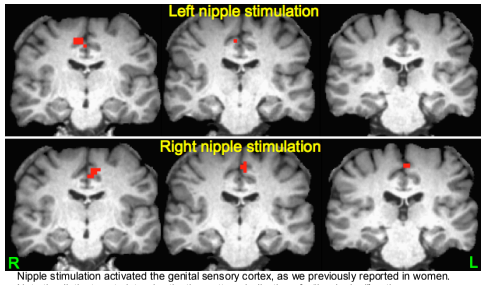

Genital innervation in men



Note partial overlap between regions activated by rectum and prostate stimulation



Specific activation produced by prostate stimulation



Nipple stimulation activated the genital sensory cortex, as we previously reported in women. Note the distinct contralateral activation pattern, indicative of a "hard-wired" pathway.

Conclusions

- **The genital sensory cortex in men**, mapped by fMRI, is located in the paracentral lobule, confirming and extending the Penfield homuncular map, which was based on electrical stimulation of brain.
- **Penis** mild, versus forceful, self-stimulation activated different, but adjacent, regions of the genital sensory cortex. This is most likely due to **dual innervation** -- differential activation of the pudendal nerve (surface skin) and the pelvic nerve (deep tissue) and their differential projections to the genital sensory cortex.
- **Testicle** self-stimulation (not mapped by Penfield) activated a different, but adjacent, region of the genital sensory cortex, different from scrotum stimulation.
- **Prostate** self-stimulation (also not mapped by Penfield) activated yet a different, also adjacent, region of the genital sensory cortex, which overlapped partially, but differed from, the regions activated by **rectum** stimulation.
- **Nipple** self-stimulation activated the genital sensory cortex, as we previously reported in women [2]. The contralateral activation provides evidence of a "hard-wired" pathway, rather than indirect via oxytocin-stimulated genital afference or via cognitive/experiential factors.
- Visceral stimulation responses tend to be located "deeper" (i.e., farther from the midline) than somatic stimulation responses.

References

1. Netter FH. The Ciba collection of medical illustrations. Nervous system. Part I. Anatomy and physiology. Summit, NJ: Ciba Pharmaceutical; 1986.____**2.** Komisaruk BR, Wise N, Frinages E, Liu W-C, Allen K, and Brody S. Women's clitoris, vagina and cervix mapped on the sensory cortex: fMRI evidence. J Sex Med 2011; 8:2822–2830.____**3.** Lots M, Wietek B, Birbaumer N, Ehrhardt J, Grodd W, Enck P. Cerebral activation during anal and rectal stimulation. Neuroimage 2001;14:1027–34.____**4.** Penfield W, Boldrey E. Somatic motor and sensory representationin the cerebral cortex of man as studied by electrical stimulation. Brain 1937;60:389–443.____**5.** Makela JP, Ilman M, Jousmaki V, Numminen J, Lehecka M, Salenius S, Forss N, Hari R. Dorsal penile nerve stimulation elicits left-hemisphere dominant activation in the second somatosensory cortex. Hum Brain Mapp 2003;18:90–9.____**6.** Nakagawa H, Namima T, Aizawa M, Uchi K, Kaiho Y,Yoshikawa S, Orikasa S, Nakasato N. Somatosensory evoked magnetic fields elicited by dorsal penile, posterior tibial, and median nerve stimulation. Electroencephalogr Clin Neurophysiol 1998; 108:57–61.____**7.** Narici L, Modena I, Opsomer RJ, Pizzella V, Romani GL, Traversa R, Rossini PM. Neuromagnetic somatosensory homunculus: A non-invasive approach in humans. Neurosci Lett 1991;2:51–4.____**8.** Allison T, McCarthy G, Luby M, Puce A, Spencer D. Localization of functional regions of human mesial cortex by somatosensory evoked potential recording and by cortical stimulation. Electroencephalogr Clin Neurophysiol 1996;100:126–40.____**9.** Holstege G, Georgiadis JR, Paans AM, Meiners LC, van der Graaf FH, Reinders AA. Brain activation during human male ejaculation. J Neurosci 2003;23:9185–93.____**10.** Kell CA, Kriegstein K, Rosler A, Kleinschmidt A, Lauf H. The sensory cortical representation of the human penis: Revisiting somatotopy in the male homunculus. J Neurosci 2005;25:5984–7.____**11.** Georgiadis J, Holstege G. Human brain activation during sexual stimulation of the penis. J Comp Neurol 2005;493:33–8.____**12.** Bradley WE, Farrell DF, Ojemann G. Human cerebrocortical potentials evoked by stimulation of the dorsal nerve of the penis. Somatosens Mot Res 1998;15:118–27.

Acknowledgments

We gratefully acknowledge the outstanding contribution of Dr. Pooja Lakshmin, MD, for the sensitive task of recruiting research participants. Support: NIH 2R25GM060826 and Rutgers University Fund.

Appendix G.2.3. An fMRI video animation time-course analysis of brain regions activated during self-stimulation to orgasm in women.

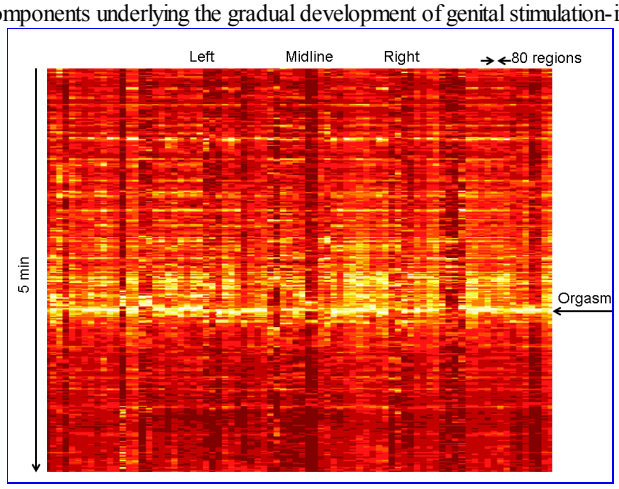
Print this Page

NEUROSCIENCE 2011

Presentation Abstract

Program#/Poster#:	495.03/SS27
Presentation Title:	An fMRI video animation time-course analysis of brain regions activated during self-stimulation to orgasm in women
Location:	Hall A-C
Presentation time:	Monday, Nov 14, 2011, 3:00 PM - 4:00 PM
Authors:	***B. R. KOMISARUK**, N. WISE, E. FRANGOS, W. BIRBANO, K. ALLEN; Dept Psychology, Rutgers, The State Univ. of New Jersey, NEWARK, NJ
Abstract:	In an fMRI analysis of genital stimulation-induced orgasm, we reported the following sequential activation of multiple brain regions: genital sensory cortex (paracentral lobule) then limbic system regions (insula, anterior cingulate, amygdala, hippocampus) then prefrontal cortex and cerebellum then hypothalamus and nucleus accumbens, followed after orgasm by an overall reduction in activity of all these brain regions. That preliminary analysis was based upon continuous fMRI recording, in which we created regions of interest (ROIs) based on Brodmann's areas, and represented the activity in each of 80 brain regions (40 on each laterality) as a rising or falling line graph over time (Komisaruk et al, SFN, 285.6, 2010). A more precise insight into the sequence of activation of these brain regions can be gained through dynamic visualization in the form of an animation video that utilizes the same form of data. Consequently, in the present analysis, we have represented the activity of each of 80 Brodmann Area ROIs in its "hot metal" analog, with 10 gradation levels progressing through red, orange, yellow to white. This color code is then applied to each ROI for each 2-sec period during the course of genital self-stimulation before, during, and after orgasm. This is represented in non-dynamic form as the matrix below (a representation of one woman's orgasm, which is similar to others'), in which each column is an ROI and each row starting from the top down is a 2-sec period. Inspection of the matrix reveals: a) non-uniform sequence of activation of different brain regions leading up to orgasm, b) greater activation in the right hemisphere than the left, c) widespread activation of the brain at orgasm, and d) substantial reduction in brain activity after orgasm. Our analytic animation method utilizes a recurrent loop

video. It facilitates an understanding of the interaction and sequential activation of the brain components underlying the gradual development of genital stimulation-induced orgasm.



Disclosures: **B.R. Komisaruk:** None. **N. Wise:** None. **E. Frangos:** None. **W. Birbano:** None. **K. Allen:** None.

Keyword(s): ORGASM

WOMAN

FMRI

Support: NIH 2R25 GM060826

Support: NIH 2R25 GM060826 and the Rutgers University Research Fund.

[Authors]. [Abstract Title]. Program No. XXX.XX. 2011 Neuroscience Meeting Planner. Washington, DC: Society for Neuroscience, 2011. Online.

An fMRI video animation time-course analysis of brain regions activated during self-stimulation to orgasm in women. #495.03/SS27

Barry R. **KOMISARUK**, Nan **WISE**, Eleni **FRANGOS**, Wendy **BIRBANO**, & Kachina **ALLEN**

Department of Psychology, Rutgers, The State University of New Jersey, Newark, NJ 07102

INTRODUCTION:

Orgasm is characterized by a gradual buildup of excitation of neural elements in the brain to a peak, followed by a subsidence. In the present study, we seek to capture that sequential pattern and depict it graphically and dynamically. Thus, we have depicted the fMRI activity of conventional brain regions (Brodmann and other areas – "ROIs") with a unitary convention ("hot metal" analog of each area's changing sequential activity) and placed each ROI's sequential activity pattern side by side, forming a graphical "tapestry". Then to represent the tapestry dynamically, we selected 20 equally-spaced moments in the sequential pattern and generated an animated film.

RESULTS:

The "tapestry" matrices show :

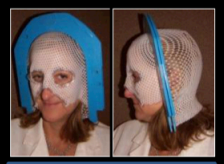
1. Non-uniform sequence of activation of different brain regions leading up to orgasm.

2. Widespread activation of the brain at orgasm.

3. Substantial subsidence in brain activity after orgasm.

iPAD

Animation generated from "snapshots" of fMRI whole-brain activity at 20 equal-interval rows of data from the accompanying "tapestry" and then "morphed" to smooth the sequence.



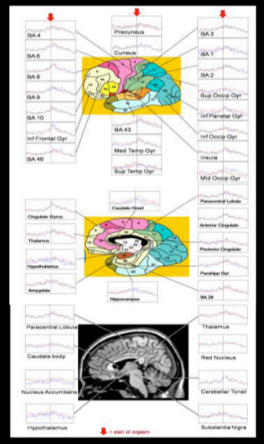
Minimizing head movement during orgasm: A thermoplastic, semi-rigid head restrainer is custom-shaped to each research participant and the blue frame is then clamped into the fMRI head cage.

METHODS:

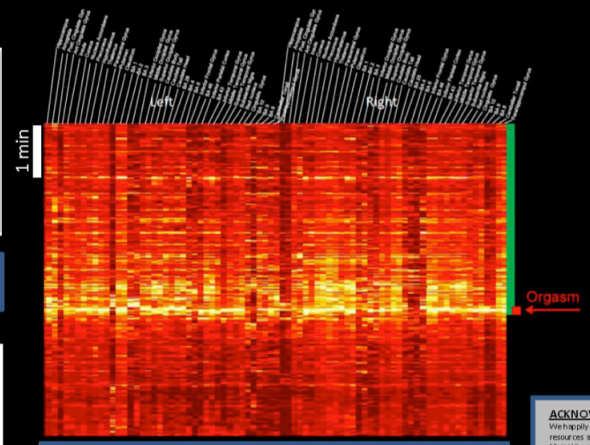
The fMRI scans were performed on a Siemens Allegra 3T at UMDNJ. AFNI was used for image analysis. The data were collected using a standard EPI sequence in a 3T Siemens Allegra scanner, TR=2 sec, TE=30 sec, voxel size: 4 x 4 x 5 mm, and 32 slices. For each subject's data, standard preprocessing was carried out using AFNI (without detrending) and data were warped to normalized space. ROIs were generated based on AFNI's Talairach (TT) Atlas. A thermoplastic head stabilization device was custom-fitted to each research participant and clamped to the head coil of the scanner to restrict head movement.

Color-coded "Tapestries"
In the present descriptive depiction of sequential fMRI activity leading up to, during, and after orgasm for each individual, we used the raw fMRI signal, not statistically analyzed. The activity of each of 80 Brodmann Area and brainstem ROIs (40 left side of brain and 40 right side) is represented as a "hot metal" analog, with 10 percentile gradation levels relative to each ROI's maximum intensity over the scan, progressing through red, orange, yellow to "white hot". This color code is then applied to each ROI for each 2-sec period during the course of genital self-stimulation before, during, and after orgasm. This is represented as the "tapestry" matrix in which each column is an ROI and each row starting from the top down is a 2-sec period. Thus, in order to emphasize the overall sequential brain pattern, we:
a) combined activity in large Brodmann and other areas (ROIs),
b) depicted the activity of each ROI in sequential 2-sec intervals,
c) depicted activity of each ROI as a percent of its maximum during the scan,
d) grouped activity into 10 graded intensity bins (0-10%, 11-20%...91-100%),
e) "hot metal" analog color-coded the intensity of the activity in the 10 graded bins.

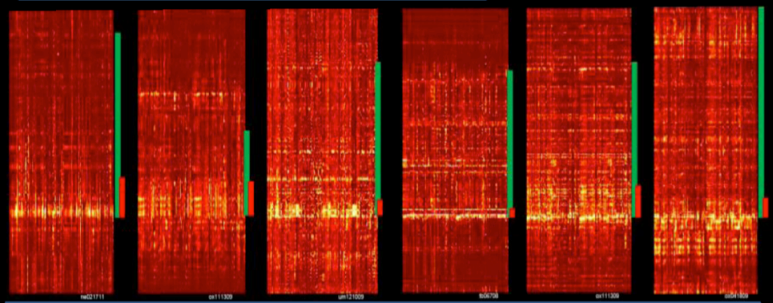
Group analysis
Mean time course activations based upon combined activity of 15 orgasms from 9 women were calculated from each ROI using AFNI's 3D ROI stats function.



Continuous regional fMRI activity at orgasm (red vertical arrows) and the 2-min periods prior to, and following, the orgasm onset (n=15 orgasms of 9 women).
Note the regional differences in the sequential excitation patterns.



"Tapestry" depiction of genital self-stimulation to an orgasm in one woman. Each of 80 labeled brain regions (ROIs) is represented by a column. Each row represents a successive 2-sec scan starting from the top. The activity in each ROI relative to its maximum during the scan is represented as a "hot metal" analog. The vertical green bar indicates when genital self-stimulation was applied. The red bar represents the onset and duration of orgasm, after which genital self-stimulation stopped. The accompanying animation is formed from 20 of these equal-interval rows (i.e., "snapshots").



Six sequences of a genital self-stimulation-induced orgasm in different women. The "tapestries" all utilize the same conventions as the larger example above. In order to facilitate comparisons, the approximate time of occurrence of the orgasms is aligned among the six samples, which necessitated "stretching" the time bases differentially along the vertical axis.

CONCLUSIONS:

The present sequential fMRI analysis depicts an *overall increase in activity throughout the brain at orgasm*, followed by an overall reduction in activity.

Different brain regions show different sequential patterns of activation.

The focus on global activity patterns limits spatial and temporal resolution.

Future connectivity analysis will be applied to identify temporal interactions among brain regions.

ACKNOWLEDGMENTS:

We happily acknowledge the great generosity of effort, time, and resources and the outstanding assistance of Alexander Tsiaras and Matt Wimsatt of The VisualMD (Anatomical Travelogue, NYC) for rendering the fMRI sequential activity and creating the animation film.
Funding support: NIH 2R25 GM060826 and the Rutgers University Research Fund.

Appendix G.2.4. An fMRI time-course analysis of brain regions activated during self-stimulation to orgasm in women

Print this Page

Presentation Abstract

Program#/Poster#:	285.6/YY4
Title:	An fMRI time-course analysis of brain regions activated during self-stimulation to orgasm in women
Location:	Halls B-H
Presentation Time:	Sunday, Nov 14, 2010, 2:00 PM - 3:00 PM
Authors:	***B. R. KOMISARUK**[1,2], N. J. WISE[1], E. FRANGOS[1], K. ALLEN[1,3]; [1]Dept Psychology, Rutgers, The State Univ. of New Jersey, NEWARK, NJ; [2]Radiology, New Jersey Med. Sch. of UMDNJ, Newark, NJ; [3]Princeton Neurosci. Inst., Princeton Univ., Princeton, NJ
Abstract:	Our previous research on genital self-stimulation in women identified brain regions that are activated during orgasm. These regions include the nucleus accumbens, anterior hypothalamus (in the region of the paraventricular nucleus), amygdala, anterior cingulate cortex, insula, hippocampus, cerebellum, and paracentral lobule. In the present study, we extend these findings by analyzing the relative time course of activation of these and other brain regions. We find evidence of differential rates of activation among more than 30 discrete anatomical areas on each of the left and right sides of the brain. Based on preliminary analysis of self-stimulation data, genital sensory cortex, thalamus, motor areas, cerebellum, hypothalamus, and substantia nigra are activated earliest. Closer to the onset of orgasm and continuing through orgasm, frontal cortical regions, entorhinal cortex, cingulate cortex, insula, amygdala, and hippocampus become activated. Later in the orgasm, and shortly thereafter, the levels of activation peak in the hypothalamus, nucleus accumbens, and caudate. Thus, leading up to, during, and after orgasm there are marked differences in the temporal profiles of activity (increases and decreases) among specific brain regions. As reported previously (Komisaruk et al, 2004, Brain Research,1024:77) activation evidently occurs in widespread regions throughout the brain during orgasm. The slow

time course of the development, duration, and resolution of orgasm (i.e., over seconds and minutes) provides a useful model to elucidate the integration of neural systems mediating the cognitive, emotional, somatic, and visceral components of this intense human experience.

Disclosures: **B.R. Komisaruk:** None. **N.J. Wise:** None. **E. Frangos:** None. **K. Allen:** None.

Keyword(s): SEXUAL BEHAVIOR

MAPPING

BRAIN IMAGING

Support: NIH 2R25 GM060826 (BRK)

Rutgers University Research Fund

[Authors]. [Abstract Title]. Program No. XXX.XX. 2010 Neuroscience Meeting Planner. San Diego, CA: Society for Neuroscience, 2010. Online.

An fMRI time-course analysis of brain regions activated during self-stimulation to orgasm in women

Barry R. Komisaruk[1,2], Nan Wise[1], Eleni Frangos[1], and Kachina Allen[1,3]

285.6 / YY4

[1]Department of Psychology, Rutgers University, Newark, NJ 07102

[2]Department of Radiology, New Jersey Medical School of the University of Medicine and Dentistry of New Jersey, Newark, NJ 07101

[3]Princeton Neuroscience Institute, Princeton University, Princeton, NJ 08544

INTRODUCTION

Orgasm is a neural process in which the effect of a sensory stimulus gradually – over minutes – increases the level of excitation of neural elements in the brain, reaching a peak of excitation and then subsides. To our knowledge, the sequence of activation of neural systems in the brain leading up to, during, and after orgasm, is not known.

In the present study, using fMRI, we extended our previous studies[1,2] by analyzing 80 brain regions repetitively at 2-second intervals during the course of genital self-stimulation-elicited orgasm, and plotted their intensity sequentially over time.

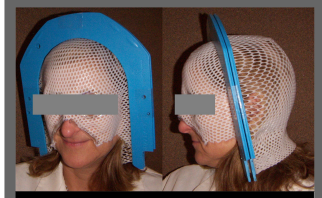
Combined data from 9 women are shown.

METHODS

The moment when each woman raised her hand to indicate the start of her orgasm was used as the group alignment point. The 2-minute period prior to, and the 2-minute period after, that moment was then plotted, as shown in the accompanying figures. The intensity of each brain region was calculated as a percent of its maximum over the course of its entire orgasm "run" and the group averages are plotted.

A total of 15 orgasms from 9 women are included in the group analysis. fMRI data were collected using a standard EPI sequence in a 3T Siemens Allegra scanner, TR=2 sec, TE=30 sec, voxel size: 4 x 4 x 5 mm, and 32 slices.

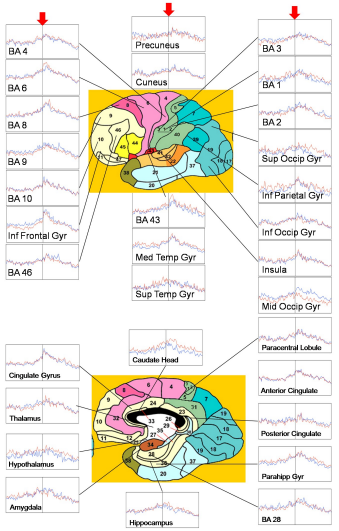
Time course data: For each subject's data, standard preprocessing was carried out using AFNI (without detrending) and data were warped to normalized space. ROIs were generated based on AFNI's Talairach (TT) Atlas and mean time course activations were calculated from each ROI using AFNI's 3D ROI stats function.



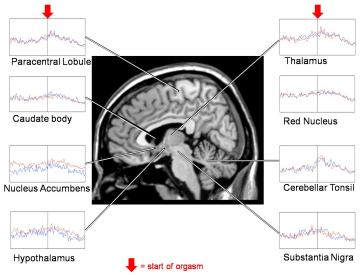
Minimizing head movement during orgasm:

A thermoplastic, semi-rigid head restrainer is custom-molded to each research participant and the blue frame is then clamped into the fMRI head cage.

Widespread forebrain regions showed similar activation patterns



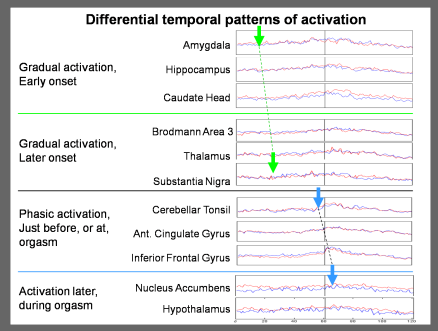
Brainstem showed differentiated activation patterns



SUMMARY:

- There was widespread activation of the brain leading up to, and during, orgasm.
- The activation occurred in a variety of temporal patterns.
- These temporal patterns of activation were more similar among telencephalic regions than among brainstem regions.
- Some brain regions showed relatively early onset of activation leading to orgasm (e.g., amygdala, hippocampus, and head of caudate) relative to brain regions that showed later onset of activation (e.g., sensory cortex, thalamus, and substantia nigra).
- Other brain regions showed an abrupt increase in activity at orgasm (e.g., anterior cingulate cortex, inferior frontal cortex, and cerebellum).
- Still other brain regions showed peak activation after the onset of orgasm (e.g., nucleus accumbens and hypothalamus).

Differential temporal patterns of activation



MOVIE

After preprocessing with AFNI, subject data were marked at significant points (start self-stimulation, start orgasm, end orgasm) and data were binned into preset time periods. From the start of stimulation to the start of orgasm, data were binned into 54 time periods and from the start of orgasm to the end of orgasm, data were binned into 10 time periods. As timing varied between subjects, the number of TRs in each bin varied among subjects. For post-orgasm times, TRs were binned into 4 second intervals. This gave a total of 264 time bins spanning each orgasm. For each bin, GLM analysis was carried out on group data. Group data were thresholded so that only the most active 6% of voxels were selected from each group image.

To generate a distribution of voxel chain lengths across time, 1000 repeats of a bootstrapping procedure were run such that 6% of voxels were randomly assigned to each time image and the likelihood of the same voxel being activated across consecutive time periods was assessed. From this distribution it was determined that a voxel needed to pass thresholding in at least 3 consecutive time periods to maintain a total corrected threshold of 0.06. Voxels not meeting this criterion were removed from the analysis. The corrected data were then spliced into a movie to graphically show activation of areas over time.

To view movie, please visit

http://psychology.rutgers.edu/~brk/

RATIONALE

The conventional GLM analysis is limited in representing small regions, spatially-distributed networks, and dynamic changes over time.

Time-course analysis is limited to concurrent events across subjects.

Thus, the analysis of orgasm by these two methods is suboptimal because the latency and duration of orgasm shows significant variation within and among subjects.

We addressed these limitations by developing an analysis method that attributes statistical significance to voxels that show temporal consistency. This has the advantage of being able to analyze small regions of activity over time.

This method provided the opportunity to "string" the "snapshots" of brain activity into a sequence, thus generating a visualization of orgasm activation over time.

CONCLUSIONS

- The rates and latencies of activation of brain regions leading up to, during, and immediately after orgasm are non-uniform; some are gradual and others are more abrupt.
- The similarities in temporal activation patterns among telencephalic regions are greater than those among brainstem regions.
- The differential, sequential, patterns of regional brain activation provide insight into the neural process underlying this gradually developing peak experience.

REFERENCES

1. Komisaruk, B. R., & Whipple, B. (2005). Functional MRI of the brain during orgasm in women. *Annual Review of Sex Research, 16*, 62.

2. Komisaruk, B. R., Whipple, B., Crawford, A., Grimes, S., Liu, W. C., Kalnin, A., & Mosier, K. (2004). Brain activation during vaginocervical self-stimulation and orgasm in women with complete spinal cord injury: FMRI evidence of mediation by the vagus nerves. *Brain Research, 1024*(1-2), 77-88.

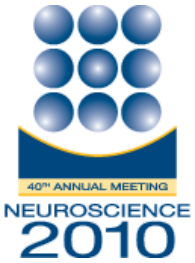
3. Komisaruk, B., Whipple, B., Crawford, A., Grimes, S., Kalnin, A., Mosier, K., Liu, W., & Hankins, B. (2002). Brain activity (fMRI and PET) during orgasm in women in response to vaginocervical self-stimulation. Abstract number 841.17. *Society for Neuroscience, Washington, DC*.

4. Komisaruk, B.R., Wise, N., Frangos, E., & Liu, W.C (2009). Women's clitoris, vagina and cervix mapped on the sensory cortex, using fMRI. Abstract number 562.18, *Society for Neuroscience, Washington, DC*.

Support: NIH 2 R 25 GM060526 and the Rutgers University Research Fund (BRK).

Appendix G.2.5. Tactile imagery somatotopically activates genital sensory homunculus: fMRI evidence.

Print this Page



Presentation Abstract

Program#/Poster#:	800.6/HHH48
Title:	Tactile imagery somatotopically activates genital sensory homunculus: fMRI evidence
Location:	Halls B-H
Presentation Time:	Wednesday, Nov 17, 2010, 9:00 AM -10:00 AM
Authors:	*N. J. WISE[1], E. FRANGOS[1], B. R. KOMISARUK[1,2]; [1]Psychology, Rutgers Univ., Newark, NJ; [2]Radiology, New Jersey Med. Sch. of UMDNJ, Newark, NJ
Abstract:	In the course of our previous study (Komisaruk et al, 2009; SFN Abstracts 562.18) in which we mapped the sensory cortical representation of the clitoris, vagina, cervix, nipple and finger, our control procedure - imagining stimulation of those specific body regions while remaining motionless - generated activity that overlapped substantially with that induced by their actual physical stimulation. That is, when the research participants were instructed to imagine the thumb being tapped, the corresponding homuncular region of the somatosensory cortex became activated. Similarly, when instructed to imagine the clitoris or the vagina being stimulated, the corresponding homuncular sensory cortical regions became activated. Moreover, in the case of each body region studied, the imagery procedure activated the sensory relay region (VPL) of the thalamus. Surprisingly, when the participants were instructed to imagine the nipple being stimulated, activations were found not only in the corresponding thoracic homuncular region, but also in the genital sensory cortical region (i.e., the paracentral lobule). Cerebellar and supplementary motor area activations were activated during the imagery procedures. In general, while there was a lower magnitude of signal intensity in response to imagery than to physical stimulation, the reverse was true in the frontal cortex. The present findings are consistent with, and extend to the genital system, recent reports of imagery-induced activation of the sensory cortices in each of the sensory systems (Yoo et al, 2003, NeuroReport,14:581; Belardinelli et al,

2009, Acta Psychol., 132:190).

Disclosures: **N.J. Wise:** None. **E. Frangos:** None. **B.R. Komisaruk:** None.

Keyword(s): SEX

SOMATOSENSORY CORTEX

MAPPING

Support: NIH 2R25 GM060826

Rutgers University Research Fund

[Authors]. [Abstract Title]. Program No. XXX.XX. 2010 Neuroscience Meeting Planner. San Diego, CA: Society for Neuroscience, 2010. Online.

Tactile imagery somatotopically activates genital sensory homunculus: fMRI evidence

Nan Wise[1], Eleni Frangos[1], and Barry R. Komisaruk [1,2]

800.6 / HHH48

[1]Department of Psychology, Rutgers University, Newark, NJ 07102 and

[2]Department of Radiology, New Jersey Medical School of the University of Medicine and Dentistry of New Jersey, Newark, NJ 07101

INTRODUCTION

Rationale for the present research: A serendipitous finding

As a control procedure for our mapping of the sensory cortical representation of the clitoris, vagina, cervix, nipple, and finger in women (Komisaruk et al., 2009: SFN Abstracts 562.18) participants were asked to imagine stimulation of those specific body regions. We were surprised to find that just "*thinking*" about specific body regions being stimulated generated activity that overlapped substantially with that induced by their actual physical stimulation in the somatosensory cortex. This observation led us to explore the phenomenon in more detail.

Background

•Yoo et al. (2003) demonstrated that tactile imagery activated corresponding regions of the primary and secondary somatosensory cortices (SI,SII).

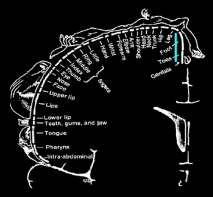
•Belardinelli et al. (2009) showed that primary sensory areas were correspondingly activated by imagery in tactile, visual, gustatory, kinesthetic, and somatic modalities.

•Brain regions activated by imagery overlap with those activated by physical sensory stimulation:

-Auditory imagery activates auditory cortex. (Yoo et al., 2001)

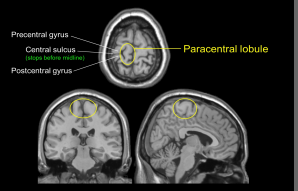
-Visual imagery activates visual cortex. (Cohen et al., 1996; Kosslyn et al., 1995)

Sensory Cortex Homunculus of Penfield and Rasmussen



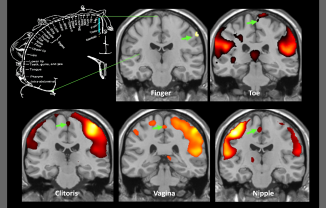
1. Sensory homunculus map based upon roving electrical stimulation of cerebral cortex in awake, locally-anesthetized **men** (only) who reported on the location of their bodily sensations (Penfield & Rasmussen, 1950).

Genital Sensory Cortex is in the Paracentral Lobule



2. Note that the **Sensory Cortex** starts laterally in the **Postcentral Gyrus** and continues medially in the **Paracentral Lobule**. Thus, the face, hands and arms are represented in the postcentral gyrus, whereas the groin, legs, feet and genitals are located in the paracentral lobule.

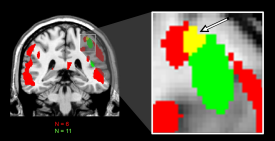
Background: Sensory Cortex in Women (N=11)



3. fMRI-based group presentation of cortical responses to the experimenter tapping their thumb or big toe (hallux), and to the women self-stimulating their clitoris, anterior vaginal wall, or nipple. Note the correspondence between the cortical regions activated by these stimuli and the map generated by Penfield. The two types of genital self-stimulation, and surprisingly, nipple stimulation, activate different, but adjacent, regions of the *Paracentral Lobule* in the medial cortex.

Finger: Postcentral Gyrus

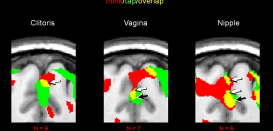
think/tap/overlap



4. Group-based composite view of the postcentral gyrus representing finger tactile imagery ("think") activation in red and finger tactile stimulation ("tap") in green. The area in yellow represents the location in which the activations for the "think" and "tap" conditions overlap.

Anterior Paracentral Lobule (🦶) / Posterior SMA (🤞)

think/tap/overlap

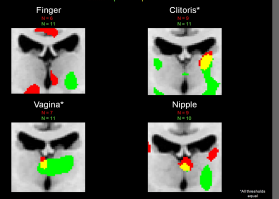


5. "*Thinking*" of stimulation of a body part and physical stimulation of that body part activate overlapping regions of the somatosensory cortex, specifically the paracentral lobule.

Consistent with, and extending, our previous report (Komisaruk et al., 2009: SFN Abstracts 562.18) "*thinking*" of nipple stimulation activates the somatosensory cortex in the region that overlaps with genital self-stimulation.

Thalamus

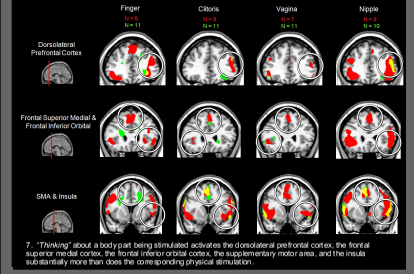
think/tap/overlap



6. Particularly surprising is the observation of sensory thalamus in response to "*thinking*" of stimulation of the specific body parts.

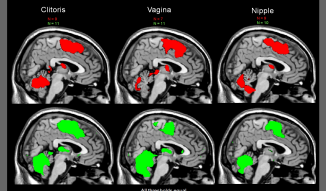
Frontal Cortex

think/tap/overlap



7. "*Thinking*" about a body part being stimulated activates the dorsolateral prefrontal cortex, the frontal superior medial cortex, the frontal inferior orbital cortex, the supplementary motor area, and the insula substantially more than does the corresponding physical stimulation.

Tap > Think: Cerebellum



8. The cerebellum was activated by both "*thinking*" and physical stimulation of these body regions, although "*thinking*" activations of the cerebellum were of a lower magnitude.

Methods

Research Participants

Eleven healthy right-handed women, ages 23-56, prescreened with the SCL-90 questionnaire and interview to ensure their psychological fitness for study participation. Participants were recruited by word of mouth. Each participant tested negative for pregnancy prior to scanning. The research protocol received approval by the NJMS-UMDNJ IRB and all fMRI scanner safety procedures were strictly followed. Each participant was compensated $100 for the study.

Experimental Paradigm

"Boxcar" experimental design, 5-min duration per trial, 30 sec ON – 30 sec OFF.

Landmark trials consisted of an experimenter rhythmically tapping a participant's thumb or toe in separate trials to establish reference points on the sensory cortex.

The current study focuses on data collected from a subset of participants inducted as an additional control condition in which participants were instructed to "*think*" about stimulation of specific body parts, counterbalanced with the actual physical stimulation of these body parts. The "*thinking*" control conditions included "*think finger*" (N=6), "*think clitoris*" (N=9), "*think vagina*" (N=7), and "*think nipple* (N=9). All data collected for the "thinking" conditions are reported.

Experimental mapping trials consisted of participants self-stimulating, with "comfortable" intensity, the clitoris, anterior wall of the vagina, the cervix, or the nipple, in separate, randomized trials. Clitoral self-stimulation was applied using rhythmical tapping with the right hand. Vaginal self-stimulation (of the anterior wall) was applied using the participants' own "G-Spot" stimulator (typically a 15mm-diameter S-shaped acrylic rounded-tip cylinder). Cervical self-stimulation was applied using a similar-diameter, glass or acrylic straight rounded-tip cylinder brought to the study by each participant. Nipple self-stimulation was applied using the right hand to tap the left nipple rhythmically.

All trials started with 30-sec rest; the participants were instructed by an experimenter via headphones as to when to start and stop self-stimulation or "thinking" about stimulation of the specific body regions.

The participants were in continuous verbal contact with the experimenters for the duration of the experimental paradigm.

fMRI acquisition

Individuals were imaged in the transaxial plane using standard functional MR imaging BOLD techniques [58]. The individuals were imaged on a 3 T Siemens Allegra system using gradient-echo echo-planar sequences (EPIBOLD) with the following acquisition parameters: 2000/40 (TR/TE); 64X64 matrix, 22 cm field of view, 5-mm-thick contiguous sections, and a 90 degree flip angle. For each 5-min sensory paradigm, 150 image sets at each of 32 slice locations were obtained using a standard quadrature "bird cage" head coil. Individuals' heads were immobilized with foam and taped to the head holder to limit motion. Images were reconstructed from Siemens proprietary software (Advanced Neuro Package) and transferred to a remote workstation for post processing and brain mapping analysis.

Anatomical images

Spin echo (TR/TE = 450/14) high-resolution anatomic images were acquired in the transaxial planes in identical slice locations during the same imaging session.

Data analysis

Statistical parametric mapping (SPM99) was utilized. In SPM99, the blood oxygenation level dependent (BOLD) [49] signal intensity of each voxel during the stimulus conditions was compared statistically with its activity during the prestimulus conditions (baseline condition). The images were pre-processed for realignment, normalization to Talairach space, and smoothness using an 8x8x10 kernel. Motion correction was applied with first-level model specification and estimation for each individual brain map. Group maps were then generated with first level analysis, since our total subject number was limited. MRIcroN was used for visualization of individual subject contrasts and group maps on a standardized anatomical template.

CONCLUSIONS

• For multiple sensory fields (finger, clitoris, vagina, nipple), brain activation produced by physical stimulation overlaps with that produced by thinking of those regions being stimulated.

• The difference between congruent and overlapping regions of brain activations may enable discrimination between real and imagined stimulation .

• The ability of "thinking" to activate the sensory thalamus implies that it is under "top-down" influence.

• The present findings contradict earlier theories (e.g., Pylyshyn 1981) that imagery and sensory perception involve unique and distinct brain regions.

LIMITATION

Reports that women have more vivid imagery than men may restrict the generalizability of the present findings as we studied only women. (e.g., Belardinelli et al., 2009)

FUTURE DIRECTION

Is there a difference among thinking of oneself stimulating one's own body part, thinking of someone else stimulating that body part, thinking of just that body part, seeing an image of that body part being stimulated, etc?

REFERENCES

Cohen, M., Kosslyn, S., Breiter, H., DiGirolamo, G., Thompson, W., Anderson, A., Bookheimer, S., Rosen, B., & Belliveau, J. (1996). Changes in cortical activity during mental rotation: A mapping study using functional MRI. *Brain, 119*(1), 89.

Komisaruk, B.R., Wise, N., Frangos, E., & Liu, W.C. (2009). Women's clitoris, vagina and cervix mapped on the sensory cortex, using fMRI. Poster presented at The Society for Neuroscience, 562.18.

Kosslyn, S. M., Thompson, W. L., Kim, I. J., & Alpert, N. M. (2000). Topographical representations of mental images in primary visual cortex. *Cognitive Neuroscience: A Reader,* 202–207.

Olivetti Belardinelli, M., Palmiero, M., Sestieri, C., Nardo, D., Di Matteo, R., Londei, A., D'Ausilio, A., Ferretti, A., Del Gratta, C., & Romani, G. (2009). An fMRI investigation on image generation in different sensory modalities: The influence of vividness. *Acta Psychologica, 132*(2), 190-200.

Penfield, W., & Rasmussen, T. (1950) The Cerebral Cortex of Man. New York: Macmillan.

Pylyshyn, Z. W. (1981). The imagery debate: Analogue media versus tacit knowledge. *Psychological Review, 88*(1), 16-45.

Yoo, S. S., Freeman, D. K., McCarthy III, J. J., & Jolesz, F. A. (2003). Neural substrates of tactile imagery: A functional MRI study. *Neuroreport, 14*(4), 581.

Yoo, S. S., Lee, C. U., & Choi, B. G. (2001). Human brain mapping of auditory imagery: Event-related functional MRI study. *Neuroreport, 12*(14), 3045.

Support: NIH 2 R 25 GM060826 and the Rutgers University Research Fund.

Appendix G.2.6. Women's clitoris, vagina and cervix mapped on the sensory cortex, using fMRI.

Print this Page

NEUROSCIENCE 2009

Presentation Abstract

Program#/Poster#:	562.18/DD35
Title:	Women's clitoris, vagina and cervix mapped on the sensory cortex, using fMRI
Location:	South Hall A
Presentation Time:	Tuesday, Oct 20, 2009, 9:00 AM -10:00 AM
Authors:	***B. R. KOMISARUK**[1,2], N. WISE[1], E. FRANGOS[1], W.-C. LIU[2]; [1]Psychology, Rutgers Univ., Newark, NJ; [2]Radiology, New Jersey Med. Sch., Newark, NJ
Abstract:	The sensory somatotopic (homuncular) representation of the body surface was originally mapped by Penfield and Rasmussen (1950) as located in the postcentral gyrus, based on electrical stimulation exclusively in men. They also reported that the foot and the genital sensory representations are situated in the medial cortex, i.e., in the "paracentral lobule," which is just superior to the cingulate gyrus. To our knowledge, women's genital regions have not been mapped on the sensory cortex. In the present study, we mapped the somatosensory cortical representation of the genital structures of 11 healthy women using fMRI in response to mechanical self-stimulation. Data were obtained using a Siemens Allegra 3T scanner with a "boxcar" stimulation paradigm (30sec-on, 30sec-off for 5min), processed and analyzed using SPM 99 and MRIcro. We hypothesized that stimulation of the specific genital structures would differentially activate the general genital region of the sensory cortex. This is based on evidence that the clitoris, vagina and cervix receive differential afferent innervation via the pudendal, pelvic, hypogastric and vagus nerves. To establish control points of reference, we also mapped the regions of the somatosensory cortex activated by finger and toe stimulation and nipple self-stimulation. Results: We found that all the genital sensory projection regions are located in the paracentral lobule, in the region just superior to the cingulate gyrus. The genital sensory regions are all located inferior to the region activated by toe stimulation, which we used as a reference point. The site activated by vaginal self-

stimulation was superior and posterior to those activated by clitoral and cervical self-stimulation. The cervical self-stimulation resulted in the strongest activation among the genital regions and was located deepest (i.e., farthest from the midline along the perpendicular to the cortical surface). Surprisingly, self-stimulation of the nipple resulted not only in activation of the thoracic sensory region, but also of the paracentral lobule within the genital sensory region. A general caveat of the interpretation of fMRI data is that the extent of activation and the degree of overlap among brain regions depends on the level of statistical significance of the threshold that is selected. Taking this caveat into account, we conclude, on the basis of the present findings, that the sensory projections of women's genitalia are clustered, yet differentiable, in the same general paracentral lobule region as indicated by Penfield and Rasmussen in men.

Disclosures: **B.R. Komisaruk**, None; **N. Wise**, None; **E. Frangos**, None; **W. Liu**, None.

Keyword(s): FEMALE

SOMATOSENSORY CORTEX

FUNCTIONAL MRI

Support: NIH Grant GM060826

Rutgers University Fund

[Authors]. [Abstract Title]. Program No. XXX.XX. 2009 Neuroscience Meeting Planner. Chicago, IL: Society for Neuroscience, 2009. Online.

Women's clitoris, vagina and cervix mapped on the sensory cortex, using fMRI

Barry R. Komisaruk[1,2], Nan Wise[1], Eleni Frangos[1], and Wen-Ching Liu[2]

562.18 / DD35

[1]Department of Psychology, Rutgers University, Newark, NJ 07102 and

[2]Department of Radiology, New Jersey Medical School of the University of Medicine and Dentistry of New Jersey, Newark, NJ 07101

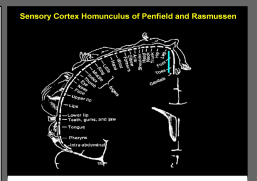
INTRODUCTION

Rationale for the present research

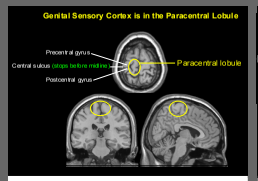
- In Penfield's classical homunculus map, the genital sensory cortex is based on penile sensation.
- Subsequent mapping of the sensory cortex by others was based on stimulation of the pudendal nerve, via the penis or the clitoris.
- However, additional nerves provide sensation to the vagina and cervix, i.e., the pelvic, hypogastric and vagus nerves (Komisaruk et al, 2004, 2006).
- To our knowledge, the projection of vagina and cervix to the sensory cortex has not been reported previously.
- **Consequently, in the present study using fMRI, we mapped the regions of the sensory cortex that are activated by clitoral, vaginal, and cervical (self-) stimulation.**
- For points of reference on the homunculus, we also mapped responses to thumb and big toe (hallux) stimulation and nipple self-stimulation.

A brief history of mapping the genital sensory cortex

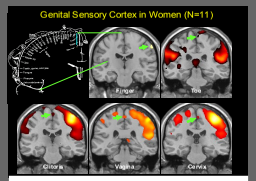
- Electrical stimulation of the brain in awake men that elicited penile sensation was represented on mesial cortex (paracentral lobule) inferior to foot representation (Foerster, 1936; Penfield & Boldrey, 1937; Penfield & Rasmussen, 1950).
- Electrical stimulation of the pudendal nerve elicited evoked potentials in the mesial cortex (Narici et al, 1991).
- Electrical stimulation of pudendal nerve in men and women activated mesial cortex representation, near the cingulate sulcus (Guerit & Opsomer, 1991; Allison et al, 1996).
- Electrical stimulation of dorsal penile (pudendal) nerve (DPN) evoked somatosensory fields midline, on the interhemispheric surface of the brain (Nakagawa et al, 1998).
- Electrical stimulation of DPN evoked cortical responses 3 cm lateral to the interhemispheric fissure and extending down into the interhemispheric fissure an additional 3 cm (Bradley et al, 1998).
- Electrical stimulation of DPN evoked somatosensory fields in the medial cortex (Meletis et al, 2003).
- Using fMRI, mechanical stimulation of the penis (by toothbrush) activated the postcentral gyrus 1 cm lateral to the medial edge of the convexity of the cortex "but did not descend along the mesial wall" (Kell et al, 2005).
- Using PET, penile stimulation by female partner activated SII but not genital SI (Georgiadis & Holstege, 2005).
- Using PET, clitoral stimulation by male partner activated SII and the "dorsal convexity" of SI (Georgiadis et al, 2006).
- Using fMRI, electrical stimulation of the clitoral nerve activated SII and "bilateral, not mesial, S1" (Michels et al, 2009).



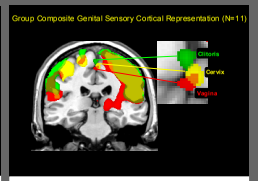
1. Sensory homunculus map based upon roving electrical stimulation of cerebral cortex in awake, locally-anesthetized **men** (only) who reported on the location of their bodily sensations (Penfield & Rasmussen, 1950).



2. Note that the **Sensory Cortex** starts laterally in the **Postcentral Gyrus** and continues medially in the **Paracentral Lobule**. Thus, the face, hands and arms are represented in the postcentral gyrus, whereas the groin, legs, feet and genitals are located in the paracentral lobule.



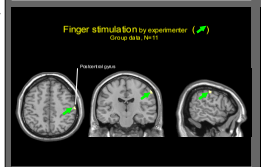
3. Present fMRI-based group presentation, in 11 **women**, of cortical responses to the experimenter tapping their thumb or their big toe (hallux), and to the women self-stimulating their clitoris, anterior vaginal wall, or uterine cervix. Note the correspondence between the cortical regions activated by these stimuli and the map generated by Penfield. The three types of genital self-stimulation activate different, but adjacent, regions of the **Paracentral Lobule** in the mesial cortex.



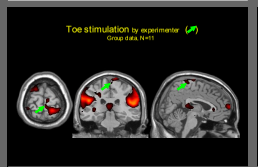
4. Group-based composite view of the clitoral, vaginal and cervical activation sites, all in the paracentral lobule, but regionally differentiated. We interpret this as due to the differential sensory innervation of these genital structures, i.e., clitoris: **pudendal** nerve, vagina: **pelvic** nerve, and cervix: **pelvic, hypogastric and vagus** nerves.

CONCLUSIONS

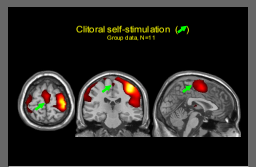
- **Clitoral, vaginal, and cervical self-stimulation** differentially activate regions of the sensory cortex, but all are **clustered in the mesial paracentral lobule.**
- Since the **perineal (groin) region** is also stimulated incidentally during the clitoral, vaginal, and cervical self-stimulation, its corresponding sensory cortical region is also activated - i.e., the **dorsal convexity of the paracentral lobule, just lateral to the midline.**
- We believe that the **present findings resolve a discrepancy in the literature** that claims that the location of the genital sensory cortical representation is on the dorsolateral cortex, rather than the mesial cortex. The discrepancy is likely due to those authors' stimulating the perineal (groin) region without adequately stimulating the genitals *per se*.
- **Unexpectedly, nipple/breast self-stimulation activated** not only the (expected) thoracic sensory cortical representation, but also the **mesial paracentral lobule**, often in sites **congruent with clitoral, vaginal, and/or cervical self-stimulation**. This finding validates women's reports that nipple/breast stimulation is erotogenic.
- We **hypothesize** that this brain response to nipple/breast self-stimulation is mediated by **oxytocin-induced afferent activity from the genital tract**. We plan to test this in women after hysterectomy.
- An intriguing **alternative hypothesis** is that nipple/breast and genital sensory activity **converge** not only on oxytocinergic neurons of the hypothalamic paraventricular nucleus but also in the genital sensory cortex.



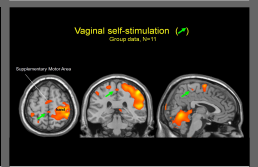
5. The group-based response to the experimenter tapping the thumb of each participant. Activation is in the **Postcentral Gyrus.** In this and the following figures, the green arrows point to the activated regions.



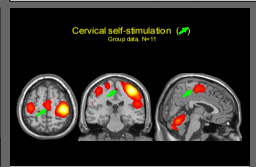
6. The group-based response to the experimenter tapping the big toe (hallux) of each participant. Activation is in the Paracentral Lobule.



7. Group-based response to the participants manually self-stimulating the **clitoris**. The arrows point to the site activated in the paracentral lobule. Note that the perineal (groin) region just lateral to the midline was also activated in this and the next 2 figures. There was marked hand-related activation in the postcentral gyrus in this and the next 2 figures. There was a continuation of activation into the supplementary motor area immediately rostral to this region in this and the next 2 figures, as well as activation extending inferiorly into SII (on the superior surface of the temporal lobe).



8. Group-based response to the participants self-stimulating the anterior wall of the **vagina** using their Lucite or glass cylinder. The arrows point to the site activated in the paracentral lobule, which is adjacent to, but below, the clitoral site.



9. Group-based response to the participants self-stimulating the uterine **cervix** using their Lucite or glass cylinder. The arrows point to the site activated in the paracentral lobule clustered with, but different from, the site activated by clitoral or vaginal self-stimulation.

METHODS

Research Participants

Eleven healthy right-handed women, ages 23-56, were prescreened with the SCL-90 questionnaire and interviewed to ensure psychological fitness for study participation. Participants were recruited by word of mouth. Each participant tested negative for pregnancy prior to scanning. The research protocol received approval by the NJMS-UMDNJ IRB and all fMRI scanner safety procedures were strictly followed. Each participant was compensated $100.

Experimental Paradigm

"Boxcar" experimental design, 5-min duration per trial, 30 sec ON – 30 sec OFF. Control trials consisted of an experimenter rhythmically tapping a participant's thumb or toe in separate trials to establish reference points on the sensory cortex. Experimental mapping trials consisted of participants self-stimulating, with "comfortable" intensity, the clitoris, anterior wall of the vagina, the cervix, or the nipple, in separate, randomized trials. Clitoral self-stimulation was applied using rhythmical tapping with the right hand. Vaginal self-stimulation (of the anterior wall) was applied using the participant's own "G-Spot" stimulator (typically a 15mm-diameter S-shaped acrylic rounded-tip cylinder). Cervical self-stimulation was applied using a similar-diameter, glass or acrylic straight rounded-tip cylinder brought to the study by each participant. Nipple self-stimulation was applied using the right hand to tap the left nipple rhythmically. All trials started with 30-sec rest; the participants were instructed by an experimenter via headphones as to when to start and stop self-stimulation. The participants were in continuous verbal contact with the experimenters for the duration of the experimental paradigm.

fMRI Acquisition

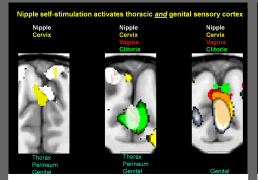
Individuals were imaged in the transaxial plane using standard functional MR imaging BOLD techniques. The individuals were imaged in a 3T Siemens Allegra system using gradient-echo echo-planar sequences (EPIBOLD) with the following acquisition parameters: 2000/40 (TR/TE); 64x64 matrix, 22 cm field of view, 5-mm thick contiguous sections, and a 90 degree flip angle. For each 5-min sensory paradigm, 150 images sets at each of 32 slice locations were obtained using a standard quadrature "bird cage" head coil. The head was immobilized with foam, and taped to limit motion. Images were reconstructed from Siemens software (Advance Neuro Package) and transferred to a remote workstation for post-processing and mapping analysis.

Anatomical Images

Spin echo (TR/TE = 450/14) high-resolution anatomical images were acquired in the transaxial planes in identical slice locations during the same imaging session.

Data analysis

SPM8 was utilized. The blood oxygenation level dependent (BOLD) signal intensity of each voxel during the stimulus conditions was compared statistically with its activity during the pre-stimulus conditions (baseline condition). The images were pre-processed, for realignment, normalized to Talairach space, and smoothed using an Bello10 kernel. Motion correction was applied with first-level model specification and estimation for each individual brain map. Group maps were then generated with first level analysis, since our total subject number was limited. MRIcro and MRIcron were used for visualization of individual subject contrasts and group maps on a standardized anatomical template.



10. **Nipple** self-stimulation activated not only the **thoracic** region, but also unexpectedly and surprisingly, the **genital** region of the paracentral lobule.

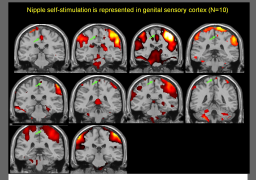
Shown are superimposed responses to nipple and genital self-stimulation in three participants.

Left panel: Note the congruence between activation produced by stimulation of nipple and cervix.

Center panel: Congruence between activation produced by stimulation of nipple, cervix and clitoris. Not unexpectedly, cervical self-stimulation activated the groin region.

Right panel: Congruence between activation produced by stimulation of nipple, vagina, cervix and clitoris.

Two surprising observations are that nipple self-stimulation also activated the groin sensory region (Left panel), and conversely, vaginal self-stimulation activated the thoracic nipple region (Center panel).



11. Individual data showing regions of the paracentral lobule that were activated by nipple self-stimulation in 9 of 10 participants. Note the variability in depth of the activated sites from the superior surface of the cortex – deeper in the top 4 cases and closer to the superior surface in the next 5 cases. The top 4 cases also indicate activation of the thoracic region (e.g., the orange arrow in the upper left case).

REFERENCES

Allison, T, McCarthy, G., Luby, M, Puce, A, & Spencer, D. (1996). Localization of functional regions of human mesial cortex by somatosensory evoked potential recording and by cortical stimulation. *Electroencephalography and Clinical Neurophysiology*, 100: 126-140.

Bradley, W. E., Farrell, D. F. & Ojemann, G. (1998). Human cerebrocortical potentials evoked by stimulation of the dorsal nerve of the penis. *Somatosensory & Motor Research*, 15(2): 119-127.

Foerster, O. (1936) Sensible corticale Felder. In: Handbuch der Neurologie, Berlin: Springer.

Georgiadis, J., & Holstege, G., (2005). Human brain activation during sexual stimulation of the penis. *The Journal of Comparative Neurology*, 493: 33-38.

Georgiadis, J., Kortekaas R., Kuipers, R., Nieuwenburg, A., Pruim, H. Reinders, S., & Holstege, G., (2006). Regional cerebral blood flow changes associated with clitorally induced orgasm in healthy women. *European Journal of Neuroscience*, 24: 3305-316.

Guerit, J.M., & Opsomer, R.J. (1991). Bit-mapped imaging of somatosensory evoked potentials after stimulation of the posterior tibial nerves and dorsal nerve of the penis/clitoris. *Electroencephalography and Clinical Neurophysiology*, 80: 228-237.

Kell, C.A, Kriegstein, K., Rosler, A., Mein schmidt, A. & Laufs, H. (2005). The sensory cortical representation of the human penis: revisiting somatotopy in the male homunculus. *The Journal of Neuroscience*, 25 (25):5984-5987.

Komisaruk, B.R., Whipple, B., Crawford, A., Grimes, S., Liu, W.-C., Kalnin, A., & Mosier, K. (2004). Brain activation during vaginocervical self-stimulation and orgasm in women with complete spinal cord injury: fMRI evidence of mediation by the Vagus nerves. *Brain Research*, 1024: 77-88.

Komisaruk, B.R., Beyer, C., and Whipple, B. (2006). The Science of Orgasm. Baltimore: The Johns Hopkins University Press.

Makela, J.P., Ilmoniemi, M., Jousmaki, V., Numminen, J., Lehecka, M., Salenius, S., Forss, N., & Hari, R. (2003). Dorsal penile nerve stimulation elicits left-hemisphere dominant activation in the second somatosensory cortex. *Human Brain Mapping*, 18: 90-99.

Michels, L., Mehnert, U., Boy, S., Schurch, B. & Kollias, S. (2009). The somatosensory representation of the human clitoris: An fMRI study. *Neuroimage*, Article in press, accepted 14 July 2009. Available on line.

Nakagawa, H., Kamima, T., Aizawa, M., Uchi, K., Kaiho, Y., Yoshikawa, S., Orikasa, S., & Nakasato, N. (1998). Somatosensory evoked magnetic fields elicited by dorsal penile, posterior tibial, and median nerve stimulation. *Electroencephalography and Clinical Neurophysiology*, 108 (1): 57-61.

Narici, L., Modena, I, Opsomer, R.J., Pizzella, V., Romani, G.L., Traversa, R., & Rossini, P.M. (1991). Neuromagnetic somatosensory homunculus: a non-invasive approach in humans. *Neuroscience Letters*, 2 (121): 51-54.

Penfield, W., & Boldrey, E. (1937). Somatic motor and sensory representation in the cerebral cortex of man as studied by electrical stimulation. *Brain*, 60: 389-443.

Penfield, W., & Rasmussen, T. (1950) The Cerebral Cortex of Man. New York: Macmillan.

Acknowledgments:

Special thanks to Ms. Gladys Martinez and Prof. Stuart Brody for their insights and help. We gratefully acknowledge Ms. Sabina Versi, Ms. Sophie Greller and Ms. Grace Maher for their excellent technical assistance.

Support: NIH 2 R 25 GM060826 and the Rutgers University Research Fund.

Appendix G.2.7. Persistent activation of vagus projections in humans after electrical stimulation of the external ear: fMRI evidence

Control/Tracking Number: 2013-A-324-NANS
Activity: Abstract
Current Date/Time: 9/24/2013 7:50:26 PM

Persistent Activation of Vagus Projections in Humans After Electrical Stimulation of the External Ear: fMRI Evidence

Author Block: Eleni Frangos, Rutgers University, Newark, NJ; Kachina Allen, Rutgers University, Newark, NJ; Nan Wise, Rutgers University, Newark, NJ; Jens Ellrich, Aalborg University, Aalborg, Denmark; Wendy Birbano, Rutgers University, Newark, NJ; Barry R. Komisaruk, Rutgers University, Newark, NJ;

Abstract:
Introduction: The present study confirms and extends our prior findings that electrical stimulation of the left concha (the concave region of the external ear immediately superior to the meatus, which is innervated by the auricular branch of the vagus nerve) activates the nucleus of the solitary tract and its projections: parabrachial nucleus, thalamus, nucleus accumbens, amygdala, and the insula. Activation was also observed in the postcentral gyrus, specifically, in the paracentral lobule (genital region), and in the locus coeruleus, periaqueductal gray, and raphe nuclei. In addition, there was a significant deactivation of the hippocampus (Frangos, E., et al. 2012, Soc. Neurosci, New Orleans, LA).
Methods: Twelve healthy participants (9 women) were scanned while mild electrical stimulation was applied for 7 minutes followed by an 11 minute “off” period to the left concha and earlobe (control). All data were analyzed using FMRIB Software Library (FSL).
Results: Time course analysis of the present data indicates a gradual increase in activation of these regions from the onset of stimulation that persisted through the 11-minute post-stimulation scan epoch.
Conclusion: The temporal pattern of the persistence differed among the brain regions. There are clinical reports that stimulation of the left vagus trunk, via electrodes implanted surgically in the neck, inhibits epileptic seizures, depression, and pain. The present finding of the hippocampal deactivation suggests a mechanism for the anti-epileptic seizure effect; the activation of the nucleus accumbens suggests a possible mechanism for the antidepressant effect; the activation of the periaqueductal gray, raphe nuclei, and locus coeruleus suggests a mechanism for analgesia. The persisting effects of t-VNS on critical vagal projections suggest that this non-invasive method can provide long-term modulation of pain, depression, epilepsy.
:

Subject Category (Complete): Peripheral Nerve Stimulation
Presentation Preference (Complete): Poster Only

Keyword (Complete): vagus ; nerve stimulation ; fMRI
Additional Info (Complete):
***Submitted to another meeting?**: No

Status: Complete

The North American Neuromodulation Society (NANS)
4700 W. Lake Avenue
Glenview, IL 60025
United States of America
Telephone: 1+847-375-4398
Fax: 1+847-375-6424
e-mail: cwelber@neuromodulation.org

Helpdesk:
Phone: 217-398-1792
Email: OASIS Helpdesk

Leave OASIS Feedback

Persistent Activation of Vagus Projections in Humans After Electrical Stimulation of the External Ear: fMRI Evidence

E. Frangos[1], K. Allen[1], N. Wise[1], J. Ellrich[2], W. Birbano[1], B. R. Komisaruk[1]

[1]Dept. of Psychology, Rutgers, The State Univ. of New Jersey, Newark, NJ; [2]Hlth. Sci. and Technol., Aalborg Univ., Aalborg, Denmark

Introduction

The auricular branch of the vagus nerve innervates the concha of the ear (a concave region of the external ear immediately superior to the meatus; Figure 1).[1] The present study extends our prior findings[2] that electrical stimulation of the left concha activates the nucleus of the solitary tract (NTS) and its projections (Figure 2).[3]

Invasive and non-invasive vagus nerve stimulation has been used therapeutically against epilepsy, chronic depression, and chronic pain.[4-8] Because left concha stimulation is applied for relatively brief periods, we hypothesized that there would be persistent effects after cessation of the stimulation period. Therefore, we measured the activity in the post-stimulation period as well.

Methods

Research Participants

Twelve healthy participants (9 females, 3 males; ages 21-71) were recruited for the study by word of mouth. The study received approval by the Rutgers University Institutional Review Board, and the "Rutgers University Brain Imaging Center (RUBIC) Common Practices for fMRI" were strictly followed. Each person was compensated for their participation.

Experimental Paradigm

Scan 1 - Control: The following fMRI data were collected in a 21-min continuous scan: 2-min rest; 1-min buccal right hand finger tap (10s on/off); 7-min left earlobe sham stimulation; 5-min rest; 5-min taste; 1-min left cheek tap.
Scan 2 - Experimental: The following fMRI data were collected in a 20-min continuous scan: 2-min rest; 7-min concha stimulation; 11-min rest.

Before each scan, participants were fitted with Cerbomed's NEMOS® device, a transcutaneous vagus nerve stimulator designed for electrical stimulation of the concha of the ear. Sham stimulation of the earlobe was conducted during the first scan by positioning the electrode upside down (Figure 3a). Concha stimulation was conducted during the second scan by positioning the electrode right side up (Figure 3b). For calibration, the stimulus intensity was increased from 0.1mA in 0.1mA increments until participants reported a "tingling" sensation that was below a noxious intensity (performed before each scan). The non-adjustable parameters of the device were continuous 0.25msec-duration monophasic square wave pulses at 25Hz. The stimulator remained in the monitor room and the 20' stimulator cable was passed through a wave guide to the subject in the scanner.

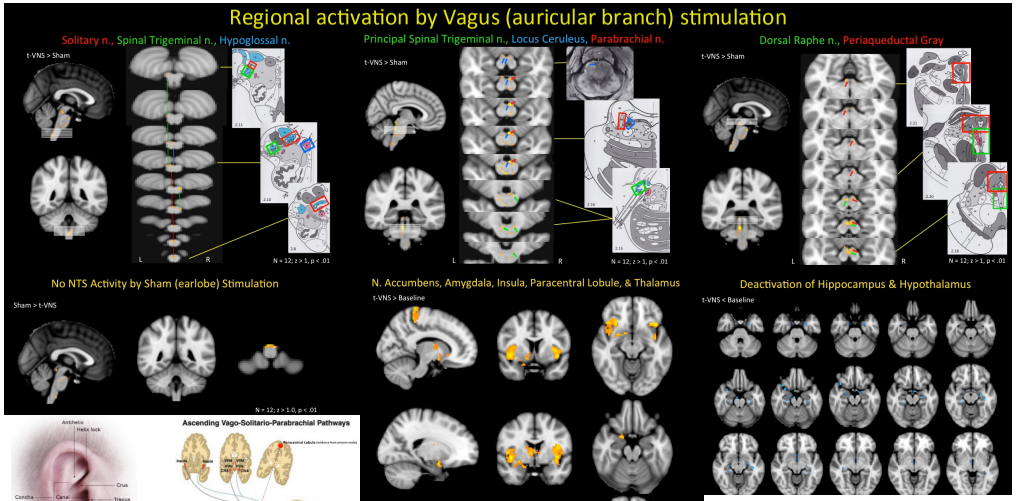
fMRI Acquisition and Data Analysis

The fMRI scans were performed at RUBIC using a 3T Siemens Trio with a 12-channel head coil. For registration purposes, anatomical images (MPRAGE) were acquired (176 slices in the sagittal plane using 1mm thick isotropic voxels, TR/TE = 1900/2.52ms, FOV = 256, 256 x 256 matrix, flip angle = 9 degrees). Fieldmaps (phase and magnitude images) were collected to correct for inhomogeneity in the magnetic field. Gradient-echo EPI sequences were acquired of the whole brain including the brainstem below the medulla (33 slices in the axial plane using 3mm isotropic voxels, TR/TE = 2000/30ms, interslice gap = 1.5 mm, flip angle = 90, FOV = 192, 64x64). The same parameters were used for the field maps with the exception of the flip angle (60) and TR/TE1/TE2 (400ms/5.19/7.65).

All data were preprocessed and statistically analyzed using FMRIB's Software Library (FSL) version 5.0.4. Lower-level analyses were carried out using FEAT. The following pre-processing steps were performed at the individual level: removal of skull and non-brain tissue from the anatomical and functional images; motion correction; spatial smoothing using a Gaussian kernel of FWHM 5mm (brainstem data were not smoothed); field inhomogeneities were corrected using B0 Unwarping in FEAT; highpass temporal filtering (gaussian-weighted least-squares straight line fitting, with σ = 630.0s for scan 1, and σ = 600.0s for scan 2). Registration of the functional images to the high-resolution anatomical images were performed using BBR followed by a non-linear registration of the high-resolution anatomical to the MNI152 standard space. Individual data were thresholded at p=0.05 (uncorrected).

Higher-level analyses were performed using FLAME 1. Masks for the following ROIs were generated using Harvard-Oxford Cortical and Subcortical Structural Atlases: amygdala, hippocampus, insula, nucleus accumbens, thalamus, and brainstem. Masks for the hypothalamus and paracentral lobule were created manually. Contrasts (t-VNS > sham and sham > t-VNS) had a cluster-forming threshold of Z>1.0 and a cluster significance threshold of p<0.01 (corrected for multiple comparisons). Sham and t-VNS comparisons to baseline had a cluster-forming threshold of Z>1.65 and a cluster significance threshold of p<0.05.

Regional activation by Vagus (auricular branch) stimulation



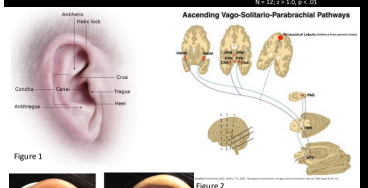


Figure 1

Figure 2

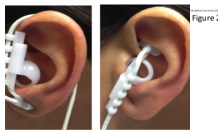
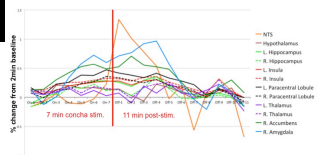


Figure 3a

Figure 3b

Preliminary Results: Time-course analysis

- A time-course analysis of the 7 min of stimulation and 11 min post-stimulation shows persistent activity of the following regions:
  - NTS, accumbens, amygdala, insula, thalamus, hippocampus, & paracentral lobule



Discussion

Electrical stimulation of the concha activated the NTS and its known projections:
Parabrachial nucleus, nucleus accumbens, insula, and amygdala.

The paracentral lobule (genital area of the sensory cortex) was also activated. Previous research provided evidence that the vagus nerve conveys vaginal and cervical afference.[9-12]
Recent evidence using fMRI showed that the vagina and cervix project to the paracentral lobule, which is the genital region of the sensory cortex.[10] This is consistent with the report that women with "complete" spinal cord injury at and above T10, which would block all known genital spinal afference through the spinal cord, were still able to feel vaginal and cervical stimulation. This observation suggested that the vagus nerves convey vaginal and cervical afferent activity to the brain, and was confirmed by fMRI evidence that the NTS was activated by vaginal and cervical stimulation in these women.[9]

A striking finding was the diametrically opposite response of the hippocampus to concha stimulation.
That is, concha stimulation *deactivated* hippocampal activity. This is consistent with the reported antiepileptic effects of stimulation of the sensory fields of the auricular branch of the vagus nerve.[5]

The activation of the nucleus accumbens suggests a possible mechanism for the antidepressant effect of concha stimulation.[8,13]

The activation of the periaqueductal gray, raphe nuclei, and locus ceruleus suggests a mechanism for the analgesic effect of concha stimulation.[6]

The present findings that the NTS and its projections were activated by concha stimulation are inconsistent with claims based on anatomical studies that the auricular branch of the vagus nerve projects to the spinal trigeminal nucleus, but not to NTS.[14,15] The functional activation of the NTS is evidently not limited to the classical anatomical projection. The two nuclei are adjacent to each other and, therefore, it is possible that afferent activity to spinal trigeminal nucleus could spread to the NTS. The significant and widespread activation in the brainstem that occurs in response to concha stimulation may be due to the non-physiological, but potentially therapeutically significant, nature of the electrical stimulation.

Conclusion

We provide fMRI evidence that the vagus input to the brain is accessible non-invasively from the external ear, specifically from the concha.

The pattern of activation and deactivation of brain regions in response to electrical stimulation of the concha provides a rational basis for the reported antiepileptic, antidepressive, and antinociceptive effects of stimulation of the auricular branch of the vagus nerve.

The persisting effects of t-VNS on critical vagal projections suggest that this non-invasive method can provide long-term modulation of pain, depression, epilepsy.

Acknowledgements

Support: Cerbomed GmbH, Erlangen, Germany; and NIH 2R25 GM 060826 (BRK).

References

1. Peuker E.T., Filler T.J. 2002. The Nerve Supply of the Human Auricle. Clin Anat. 15(1):35-7. __2. Frangos, E., Ellrich, J., Dell'Italia, J., Wise, N., Komisaruk, B. R. (2012, October). *Activation of human vagus nerve afferent projections via electrical stimulation of external ear: fMRI evidence.* Poster presented at the annual meeting of the Society for Neuroscience, New Orleans, LA. __3. Henry, T.R. 2002. Therapeutic mechanisms of vagus nerve stimulation. Neurol. 59(6 Suppl 4):53-14. __4. Ward H.E. Jr, Ninan P.T., Pollack M., Nahas Z., Anderson B., Kose S., Howland R.H., Goodman W.K., Ballenger J.C. 2008. A pilot study of vagus nerve stimulation (VNS) for treatment-resistant anxiety disorders. Brain Stimul. 1(2):112-21. __5. Stefan H., Kreiselmeyer G., Kerling F., et al. 2012. Transcutaneous vagus nerve stimulation (t-VNS) in pharmacoresistant epilepsies: a proof of concept trial. Epilepsia. 53(7):e115-8. __6. Busch V., Zeman F., Heckel A., Menne F., Ellrich J., Eichhammer P. 2013. The effect of transcutaneous vagus nerve stimulation on pain perception - An experimental study. Brain Stimul. 6(2):202-9. __7. DeGiorgio C.M., Schachter S.C., Handforth A., et al. 2000. Prospective long-term study of vagus nerve stimulation for the treatment of refractory seizures. Epilepsia. 41(9):1195-200. __8. Cristancho P., Cristancho M.A., Baltuch G.H., Thase M.E., O'Reardon J.P. 2011. Effectiveness and safety of vagus nerve stimulation for severe treatment-resistant major depression in clinical practice after FDA approval: outcomes at 1 year. 72(10):1376-82. __9. Komisaruk B.R., Whipple B., Crawford A., Grimes S., Liu W-C., Kalnin A., and Mosier K. 2004. Brain activation during vaginocervical self-stimulation and orgasm in women with complete spinal cord injury: fMRI evidence of mediation by the Vagus nerves. Brain Research. 1024:77-88. __10. Komisaruk B.R., Wise N., Frangos E., Liu, W-C, Whipple B., and Brody, S. 2011 Women's clitoris, vagina and cervix mapped on the sensory cortex, using fMRI. J Sexual Medicine. 8: 2822-2830. __11. Cueva-Rolon R., Sansone G., Bianca R., Gomez L.E., Beyer C., Whipple B., and Komisaruk B.R. 1996. Vagotomy blocks responses to vaginocervical stimulation after genitospinal neurectomy in rats. Physiology and Behavior. 60:19-24. __12. Moos F., Richard P. 1975. Level of oxytocin release induced by vaginal dilatation (Ferguson reflex) and vagal stimulation (vago-pituitary reflex) in lactating rats (author's transl). J Physiol (Paris). 70(3):307-14. __13. Kraus T., Hösl K, Kiess O., Schanze A., Kornhuber J., Forster C. 2007. BOLD fMRI deactivation of limbic and temporal brain structures and mood enhancing effect by transcutaneous vagus nerve stimulation. J Neural Transm. 114(11):1485-93. __14. Felten D.L., Jozefowicz R. (2003). Netter's Atlas of Human Neuroscience. Teterboro: Icon Learning Systems LLC. __15. Naidich TP, Duvernoy HM, Delman BN, Sorensen AG, Kollias SS, Haacke EM. (2009). Duvernoy's Atlas of the Human Brain Stem and Cerebellum. Vienna: Springer-Verlag.

Appendix G.2.8. Activation of vagus projections in humans via electrical stimulation of the external ear: fMRI time course analysis

Print this Page

Neuroscience 2013

Presentation Abstract

Program#/Poster#:	809.16/H11
Presentation Title:	Activation of vagus projections in humans via electrical stimulation of the external ear: fMRI time course analysis
Location:	Halls B-H
Presentation time:	Wednesday, Nov 13, 2013, 4:00 PM - 5:00 PM
Topic:	++D.18.a. Neurophysiology: Non-invasive mechanisms
Authors:	***E. FRANGOS**[1], K. ALLEN[1], N. WISE[1], J. ELLRICH[2,3], W. BIRBANO[1], B. R. KOMISARUK[1]; [1]Dept. of Psychology, Rutgers, The State Univ. of New Jersey, Newark, NJ; [2]Cerbomed GmbH, Erlangen, Germany; [3]Hlth. Sci. and Technol., Aalborg Univ., Aalborg, Denmark
Abstract:	The present study confirms and extends our prior findings that electrical stimulation of the left concha (the concave region of the external ear immediately superior to the meatus, which is innervated by the auricular branch of the vagus nerve) activates the nucleus of the solitary tract and its projections: thalamic VPM, nucleus accumbens, amygdala, anterior hypothalamus (region of the paraventricular nucleus), and the insula. Activation was observed in the postcentral gyrus, specifically, in the paracentral lobule (genital region) and the thoracic region. In addition, there was a significant deactivation of the hippocampus. (Frangos, E., et al. 2012, October. Activation of human vagus nerve afferent projections via electrical stimulation of external ear: fMRI evidence. Poster presented at the annual meeting of the Society for Neuroscience, New Orleans, LA.) Time course analysis of the present data indicates a gradual increase in activation of these regions from the onset of stimulation and persisting through the 11-minute post-stimulation scan epoch. Conclusions: The significant deactivation of the hippocampus suggests a mechanism by which vagal stimulation attenuates epileptic activity. There are clinical reports that stimulation of the left vagus trunk,

via electrodes implanted surgically in the neck, provides therapeutic benefit against epilepsy, depression, and pain. This type of electrical stimulation of the external ear, i.e., “transcutaneous vagus nerve stimulation”, which is currently used therapeutically, evidently provides non-invasive access to the vagus nerve and its projections.

Disclosures: **E. Frangos:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Cerbomed GmbH. **K. Allen:** None. **N. Wise:** None. **J. Ellrich:** A. Employment/Salary (full or part-time):; Cerbomed GmbH. **W. Birbano:** None. **B.R. Komisaruk:** F. Consulting Fees (e.g., advisory boards); Cerbomed GmbH.

Keyword(s): VAGUS

FMRI

ELECTRICAL STIMULATION

Support: NIH-NIGMS NIH 5 R 25 GM 096161-02

Cerbomed GmbH

Activation of vagus projections in humans via electrical stimulation of the external ear: fMRI time course analysis

E. FRANGOS[1], K. ALLEN[1], N. WISE[1], J. ELLRICH[2,3], W. BIRBANO[1], B. R. KOMISARUK[1]

[1]Dept. of Psychology, Rutgers, The State Univ. of New Jersey, Newark, NJ;

[2]Cerbomed GmbH, Erlangen, Germany; [3]Hlth. Sci. and Technol., Aalborg Univ., Aalborg, Denmark

809.16/H11

Introduction

The auricular branch of the vagus nerve innervates the concha of the ear (a concave region of the external ear immediately superior to the meatus; Figure 1).[1] The present study extends our prior findings[2] that electrical stimulation of the left concha activates the nucleus of the solitary tract (NTS) and its projections (Figure 2).[3]

Invasive and non-invasive vagus nerve stimulation has been used therapeutically against epilepsy, chronic depression, and chronic pain.[4-6] Because left concha stimulation is applied for relatively brief periods, we hypothesized that there would be persistent effects after cessation of the stimulation period. Therefore, we measured the activity in the post-stimulation period as well.

Methods

Research Participants

Twelve healthy participants (9 females, 3 males; ages 21-71) were recruited for the study by word of mouth. The study received approval by the Rutgers University Institutional Review Board, and the "Rutgers University Brain Imaging Center (RUBIC) Common Practices for fMRI" were strictly followed. Each person was compensated for their participation.

Experimental Paradigm

Scan 1 - Control: The following fMRI data were collected in a 21-min continuous scan: 2-min rest; 1-min boxcar right hand finger tap (10s on/off); 7-min left earlobe sham stimulation; 5-min rest; 5-min taste; 1-min left cheek tap.

Scan 2 - Experimental: The following fMRI data were collected in a 20-min continuous scan: 2-min rest; 7-min concha stimulation; 11-min rest.

Before each scan, participants were fitted with Cerbomed's NEMOS® device, a transcutaneous vagus nerve stimulator designed for electrical stimulation of the concha of the ear. Sham stimulation of the earlobe was conducted during the first scan by positioning the electrode upside down (Figure 3a). Concha stimulation was conducted during the second scan by positioning the electrode right side up (Figure 3b). For calibration, the stimulus intensity was increased from 0.1mA in 0.1mA increments until participants reported a "tingling" sensation that was below a noxious intensity (performed before each scan). The non-adjustable parameters of the device were continuous 0.25msec-duration monophasic square wave pulses at 25Hz. The stimulator remained in the monitor room and the 2/7 stimulator cable was passed through a wave guide to the subject in the scanner.

fMRI Acquisition and Data Analysis

The fMRI scans were performed at RUBIC using a 3T Siemens Trio with a 12-channel head coil. For registration purposes, anatomical images (MPRAGE) were acquired (176 slices in the sagittal plane using 1mm thick isotropic voxels, TR/TE = 1900/2.52ms, FOV = 256, 256 x 256 matrix, flip angle = 9 degrees). Fieldmaps (phase and magnitude images) were collected to correct for inhomogeneity in the magnetic field. Gradient-echo EPI sequences were acquired of the whole brain including the brainstem below the medulla (33 slices in the axial plane using 3mm isotropic voxels, TR/TE = 2000/30ms, interslice gap = 1.5 mm, flip angle = 90, FOV = 192, 64x64). The same parameters were used for the field maps with the exception of the flip angle (60) and TR/TE1/TE2 (400ms/5.19/7.65).

All data were preprocessed and statistically analyzed using FMRIB's Software Library (FSL), version 5.0.4. Lower-level analyses were carried out using FEAT. The following pre-processing steps were performed at the individual level: removal of skull and non-brain tissue from the anatomical and functional images; motion correction; spatial smoothing using a Gaussian kernel of FWHM 5mm (brainstem data were not smoothed); field inhomogeneities were corrected using B0 Unwarping in FEAT; highpass temporal filtering (gaussian-weighted least-squares straight line fitting, with σ = 630.0s for scan 1, and σ = 600.0s for scan 2). Registration of the functional images to the high-resolution anatomical images were performed using BBR followed by a non-linear registration of the high-resolution anatomical to the MNI152 standard space. Individual data were thresholded at p=0.05 (uncorrected).

Higher-level analyses were performed using FLAME 1. Masks for the following ROIs were generated using Harvard-Oxford Cortical and Subcortical Structural Atlases: amygdala, hippocampus, insula, nucleus accumbens, thalamus, and brainstem. Masks for the hypothalamus and paracentral lobule were created manually. Contrasts (t-VNS > sham and sham > t-VNS) had a cluster-forming threshold of Z>1.0 and a cluster significance threshold of p<0.01 (corrected for multiple comparisons). Sham and t-VNS comparisons to baseline had a cluster-forming threshold of Z>1.65 and a cluster significance threshold of p<0.05.

Results

Electrical stimulation of the concha produced activation of brainstem regions consistent with: solitary nucleus (NTS), spinal trigeminal nucleus, hypoglossal, locus ceruleus, parabrachial nucleus, dorsal raphe nucleus, and the periaqueductal gray matter(PAG).

Also activated were NTS projections: nucleus accumbens, thalamus, insula, and amygdala. Paracentral lobule (the genital sensory cortex) was also activated.

Deactivations, based on concha minus baseline, were observed in the hippocampus and hypothalamus.

Control: electrical stimulation of the earlobe did not produce activation of the NTS, although ventral medulla and the right insula were activated (not pictured).

Time-course analysis: Activity persisted after concha stimulation in: NTS, nucleus accumbens, amygdala, insula, thalamus, hippocampus, and paracentral lobule.

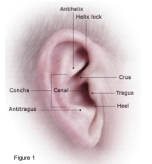


Figure 1

Ascending Vago-Solitario-Parabrachial Pathways

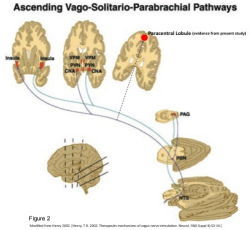


Figure 2

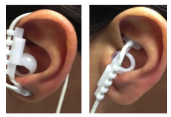
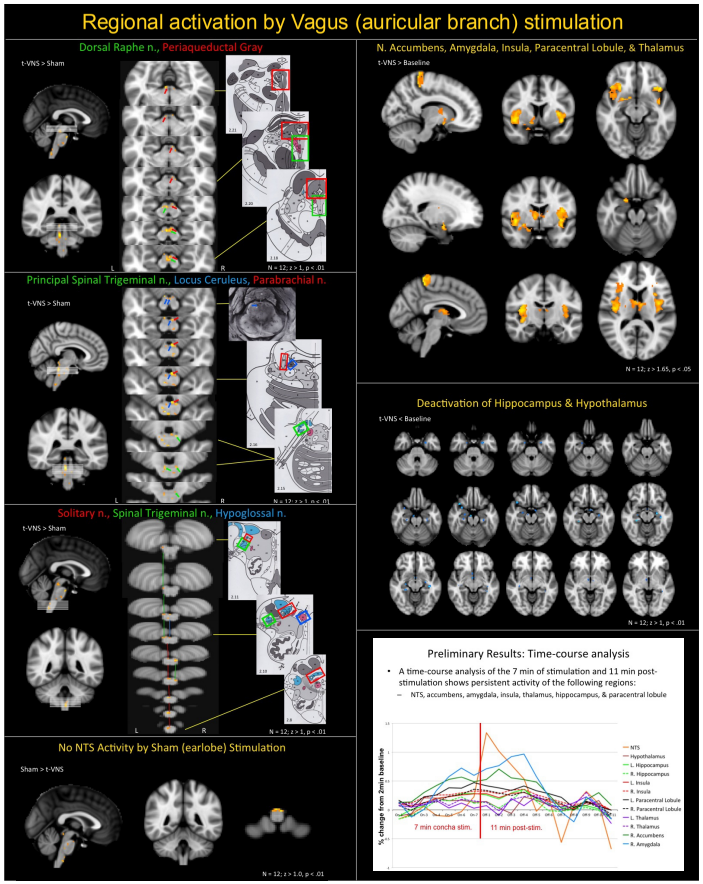


Figure 3a Figure 3b



Discussion

Electrical stimulation of the concha activated the NTS and its known projections:

- Parabrachial nucleus, nucleus accumbens, insula, and amygdala.

The paracentral lobule (genital area of the sensory cortex) was also activated. Previous research provided evidence that the vagus nerve conveys vaginal and cervical afference.[9-12]

- Recent evidence using fMRI showed that the vagina and cervix project to the paracentral lobule, which is the genital region of the sensory cortex.[10] This is consistent with the report that women with "complete" spinal cord injury at and above T10, which would block all known genital spinal afference through the spinal cord, were still able to feel vaginal and cervical stimulation. This observation suggested that the vagus nerves convey vaginal and cervical afferent activity to the brain, and was confirmed by fMRI evidence that the NTS was activated by vaginal and cervical stimulation in these women.[9]

A striking finding was the diametrically opposite response of the hippocampus to concha stimulation.

- That is, concha stimulation *deactivated* hippocampal activity. This is consistent with the reported antiepileptic effects of stimulation of the sensory fields of the auricular branch of the vagus nerve.[5]

The activation of the nucleus accumbens suggests a possible mechanism for the antidepressant effect of concha stimulation.[8,13]

The activation of the periaqueductal gray, raphe nuclei, and locus ceruleus suggests a mechanism for the analgesic effect of concha stimulation.[6]

The present findings that the NTS and its projections were activated by concha stimulation are inconsistent with claims based on anatomical studies that the auricular branch of the vagus nerve projects to the spinal trigeminal nucleus, but not to NTS.[14,15] The functional activation of the NTS is evidently not limited to the classical anatomical projection. The two nuclei are adjacent to each other and, therefore, it is possible that afferent activity to spinal trigeminal nucleus could spread to the NTS. The significant and widespread activation in the brainstem that occurs in response to concha stimulation may be due to the non-physiological, but potentially therapeutically significant, nature of the electrical stimulation.

Conclusion

We provide fMRI evidence that the vagus input to the brain is accessible non-invasively from the external ear, specifically from the concha.

The pattern of activation and deactivation of brain regions in response to electrical stimulation of the concha provides a rational basis for the reported antiepileptic, antidepressive, and antinociceptive effects of stimulation of the auricular branch of the vagus nerve.

The persisting effects of t-VNS on critical vagal projections suggest that this non-invasive method can provide long-term modulation of pain, depression, epilepsy.

Acknowledgements

Support: Cerbomed GmbH, Erlangen, Germany; and NIH 2R25 GM 060826 (BRK).

References

1. Peuker E.T., Filler T.J. 2002. The Nerve Supply of the Human Auricle. Clin Anat. 15(1):35-7.
2. Frangos, E., Ellrich, J., Dell'Italia, J., Wise, N., Komisaruk, B. R. (2012, October). *Activation of human vagus nerve afferent projections via electrical stimulation of external ear: fMRI evidence.* Poster presented at the annual meeting of the Society for Neuroscience, New Orleans, LA.
3. Henry, T.R. 2002. Therapeutic mechanisms of vagus nerve stimulation. Neurol. 59(6 Suppl 4):S3-14.
4. Ward H.E., Jr. Hinan P.T., Portack M., Nahas Z., Anderson B., Koss S., Howland R.H., Goodman W.K., Ballenger J.C. 2008. A pilot study of vagus nerve stimulation (VNS) for treatment-resistant anxiety disorders. Brain Stimul. 1 (2):112-21.
5. Stefan H, Kreiselmeyer G, Kerling F, et al. 2012. Transcutaneous vagus nerve stimulation (t-VNS) in pharmacoresistant epilepsies: a proof of concept trial. Epilepsia. 53(7):e115-8.
6. Busch V., Zeman F., Heckel A., Menne F., Ellrich J., Eichhammer P. 2013. The effect of transcutaneous vagus nerve stimulation on pain perception--An experimental study. Brain Stimul. 6(2):202-9.
7. DeGiorgio C.M., Schachter S.C., Handforth A., et al. 2000. Prospective long-term study of vagus nerve stimulation for the treatment of refractory seizures. Epilepsia. 41(9):1195-200.
8. Cristancho P., Cristancho M.A., Baltuch G.H., Thase M.E., O'Reardon J.P. 2011. Effectiveness and safety of vagus nerve stimulation for severe treatment-resistant major depression in clinical practice after FDA approval: outcomes at 1 year. 72(10):1376-82.
9. Komisaruk B.R., Whipple B., Crawford A., Grimes S., Liu W-C., Kalnin A., and Mosier K. 2004. Brain activation during vaginocervical self-stimulation and orgasm in women with complete spinal cord injury: fMRI evidence of mediation by the Vagus nerves. Brain Research. 1024:77-88.
10. Komisaruk B.R., Wise N., Frangos E., Liu W-C, Whipple B., and Brody, S. 2011 Women's clitoris, vagina and cervix mapped on the sensory cortex, using fMRI. J Sexual Medicine. 8:2823-2830.
11. Cueva-Rolón R., Sansone G., Blanco R., Gomez L.E., Beyer C., Whipple B. and Komisaruk B.R. 1996. Vagotomy blocks responses to vaginocervical stimulation after genitospinal neurectomy in rats. Physiology and Behavior. 60:19-24.
12. Moss F., Richard P. 1975. Level of oxytocin release induced by vaginal dilation (Ferguson reflex) and vaginal stimulation (vago-pituitary reflex) in lactating rats (author's transl). J Physiol (Paris). 70(3):307-14.
13. Klaus T., Holst K, Kiese G., Schanze A., Kornhuber J., Forster C. 2007. BOLD fMRI deactivation of limbic and temporal brain structures and mood enhancing effect by transcutaneous vagus nerve stimulation. J Neural Transm. 114(11):1485-93.
14. Patten D.L., Jodelle G.R. (2003). *Netter's Atlas of Human Neuroscience.* Teterboro: Icon Learning Systems LLC.
15. Naidich T.P., Duvernoy H.M., Delman B.N., Sorensen A.G., Kollias S.S., Haacke E.M. (2009). Duvernoy's Atlas of the Human Brain Stem and Cerebellum. Vienna: Springer-Verlag.

Appendix G.2.9. Activation of human vagus nerve afferent projections via electrical stimulation of external ear: fMRI evidence.

Print this Page

NEUROSCIENCE 2012

Presentation Abstract

Program#/Poster#:	891.09/MM17
Presentation Title:	Activation of human vagus nerve afferent projections via electrical stimulation of external ear: fMRI evidence.
Location:	Hall F-J
Presentation time:	Wednesday, Oct 17, 2012, 1:00 PM - 2:00 PM
Authors:	*E. FRANGOS[1], J. ELLRICH[2,3], J. DELL'ITALIA[1], N. WISE[1], B. R. KOMISARUK[1]; [1]Dept. of Psychology, Rutgers, The State Univ. of New Jersey, Newark, NJ; [2]Cerbomed GmbH, Erlangen, Germany; [3]Hlth. Sci. and Technol., Aalborg Univ., Aalborg, Denmark
Abstract:	There is anatomical evidence that a branch of the vagus nerve provides sensory innervation of the external ear. More specifically, the auricular branch of the vagus innervates the concha, which is the concave region immediately superior to the external meatus of the ear. Premise: The question addressed in the present study is whether brain regions to which vagal afferents are known to project (e.g., solitary nucleus [NTS]) can be accessed via electrical stimulation of this peripheral branch of the vagus nerve in humans. Methods: We identified activated brain regions using functional MRI. We verified the location of the NTS in the medulla oblongata by administration of a gustatory stimulus (1 cc sauce of lime juice, sugar, salt and mustard). We localized and differentiated this nucleus from the laterally adjacent nucleus cuneatus by the subjects' tapping their fingers for 40sec. Electrical stimulation of the concha of the subjects' left ear was applied using the battery-driven NEMOS® device manufactured by Cerbomed. The stimulus intensity was increased from 0.1mA in 0.1mA increments until the subjects reported a "tingling" sensation that was below noxious intensity, typically below 1mA. The non-adjustable stimulation parameters of the device were continuous 0.25msec-duration monophasic square wave pulses at 25Hz. After a 20 sec baseline resting period, the stimulation was applied continuously for 7 min,

followed by a 25 min rest period. The fMRI data were analyzed using FSL (FMRIB Software Library). Results (preliminary): Brain regions with clearly delineated landmarks activated by the electrical stimulation included: NTS, raphe nuclei, thalamic VPM, nucleus accumbens, amygdala, hippocampus, insula, and postcentral gyrus - paracentral lobule (genital) and thoracic homuncular zones. Activation was also observed in the regions of the anterior hypothalamus (paraventricular nucleus), substantia nigra, and locus coeruleus. Each of the 5 subjects tested spontaneously volunteered comments that they felt particularly relaxed after the stimulation period. Conclusion: There are clinical reports that stimulation of the left vagus trunk via electrodes implanted surgically in the neck provides therapeutic benefit against epilepsy, depression and pain. The present findings suggest that because electrical stimulation of the external ear activates the major projections of the vagus nerve, the present method of vagal stimulation could provide a less invasive therapeutic alternative.

Disclosures: **E. Frangos:** Other Research Support; Cerbomed GmbH, Erlangen, Germany. Consultant/Advisory Board; Cerbomed GmbH, Erlangen, Germany. **J. Ellrich:** Employment; Cerbomed GmbH, Erlangen, Germany. **J. Dell'Italia:** Other Research Support; Cerbomed, GmbH, Erlangen, Germany. **N. Wise:** Other Research Support; Cerbomed GmbH, Erlangen, Germany. **B.R. Komisaruk:** Other Research Support; Cerbomed GmbH, Erlangen, Germany. Consultant/Advisory Board; Cerbomed GmbH, Erlangen, Germany.

Keyword(s): VAGUS

ELECTRICAL STIMULATION

FMRI

Support: Cerbomed GmbH Research Support

NIH - NIGMS 2R25 GM060826

[Authors]. [Abstract Title]. Program No. XXX.XX. 2012 Neuroscience Meeting Planner. New Orleans, LA: Society for Neuroscience, 2012. Online.

Activation of human vagus nerve afferent projections via electrical stimulation of external ear: fMRI evidence

891.09 / MM17

E. FRANGOS[1], J. ELLRICH[2,3], J. DELL'ITALIA[1], N. WISE[1], B. R. KOMISARUK[1]

[1]Dept. of Psychology, Rutgers, The State Univ. of New Jersey, Newark, NJ;

[2]Cerbomed GmbH, Erlangen, Germany; [3]Hlth. Sci. and Technol., Aalborg Univ., Aalborg, Denmark

Introduction

The goal of the present study is to ascertain, with the use of fMRI, whether electrical stimulation of the concha, which is innervated by the (sensory) auricular branch of the vagus nerve, activates the solitary nucleus (NTS) and its projections. This would validate the use of ear stimulation as a more accessible, less invasive method of stimulating the vagus nerve. Invasive and non-invasive vagus nerve stimulation has been used against depression, epilepsy, and pain.[1-5]

There is anatomical evidence that a branch of the vagus nerve provides sensory innervation of the external ear.[6] More specifically, the auricular branch of the vagus innervates the concha, which is the concave region immediately superior to the external meatus of the ear (Figure 1).

Methods

Research Participants

Seven healthy participants (5 females, 2 males; ages 21-71) were recruited for the study by word of mouth. The study received approval by the Rutgers University Institutional Review Board, and the "Rutgers University Brain Imaging Center (RUBIC) Common Practices for fMRI" were strictly followed. Each participant was compensated $150.

Experimental Paradigm

Scan 1 - Control: The following fMRI data were collected in a 21-min continuous scan: 2-min rest; 1-min boxcar right hand finger tap (10s on/off); 7-min left earlobe sham stimulation; 5-min rest; 5-min taste; 1-min left cheek tap (N=5).

Scan 2 - Experimental: The following fMRI data were collected in a 20-min continuous scan: 2-min rest; 7-min concha stimulation; 11-min rest.

Before each scan, participants were fitted with Cerbomed's NEMOS® device (Figure 2), a transcutaneous vagus nerve stimulator designed for electrical stimulation of the concha of the ear. Sham stimulation of the earlobe was conducted during the first scan by positioning the electrode upside down (Figure 3a). Concha stimulation was conducted during the second scan by positioning the electrode right side up (Figure 3b). For calibration, the stimulus intensity was increased from 0.1mA in 0.1mA increments until participants reported a "tingling" sensation that was below a noxious intensity (performed before each scan). The non-adjustable parameters of the device were continuous 0.25msec-duration monophasic square wave pulses at 25Hz. The stimulator remained in the monitor room and the 20' stimulator cable was passed through a wave guide to the subject in the scanner.

fMRI Acquisition and Data Analysis

The fMRI scans were collected at RUBIC using a 3T Siemens Trio. Standard MPRAGE and field maps were collected. The EPIBOLD sequences were acquired in the transaxial plane, 33 3mm slices, TR=2, TE=30, using a 12-channel head coil. All data were brain extracted and registered to the MNI152 standard template using FMRIB's Software Library (FSL) Brain Extraction Tool (BET) and FMRIB's Linear Image Registration Tool (FLIRT), respectively. Lower-level fMRI data processing was carried out using FSL's FMRI Expert Analysis Tool (FEAT). The following pre-statistics processing was applied: motion correction using MCFLIRT;[7] spatial smoothing using a Gaussian kernel of FWHM 5mm; grand-mean intensity normalization of the entire 4D dataset by a single multiplicative factor; highpass temporal filtering (Gaussian-weighted least-squares straight line fitting, with sigma=630.0s). For statistical processing, Z (Gaussianised T/F) statistic images were thresholded at P=0.05 (uncorrected). Higher-level fMRI data processing was carried out using FSL's FEAT. Masks for the regions of interest (ROIs) were generated using Harvard-Oxford Cortical and Subcortical Structural Atlases. Z (Gaussianised T/F) statistic images were thresholded using clusters determined by Z>1 and a (corrected) cluster significance threshold of P=0.05.[8]

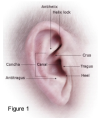


Figure 1

Figure 2

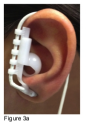


Figure 3a

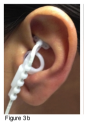


Figure 3b

Results

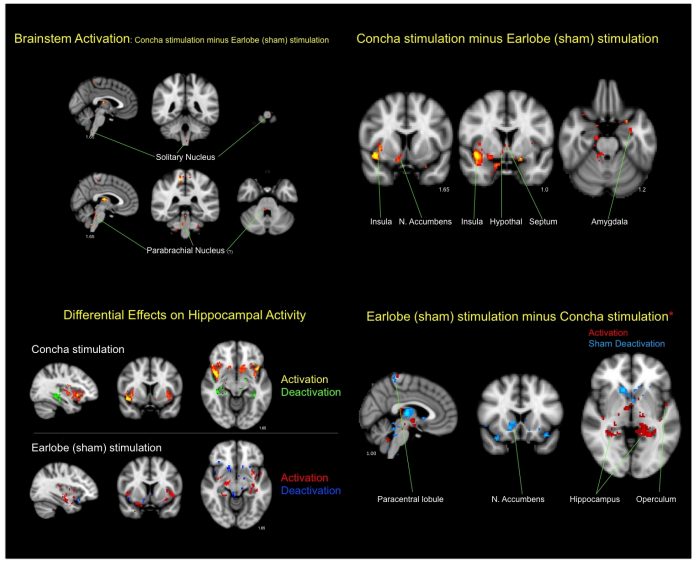
As summarized in the brain images:

Electrical stimulation of the concha produced activation of the following regions (based on analysis of concha stimulation minus earlobe [sham] stimulation): solitary nucleus (NTS) and its following projections: parabrachial nucleus, nucleus accumbens, hypothalamus, thalamus, amygdala. In addition, paracentral lobule, and insula were activated.

Deactivation, based on analysis of concha against baseline, was observed in hippocampus.

Electrical stimulation of the earlobe produced activation of the following regions (based on analysis of earlobe stimulation minus concha stimulation): hippocampus, operculum, thalamus, small (non-genital) region of the paracentral lobule.

Deactivation, based on analysis of sham against baseline, was observed in nucleus accumbens, paracentral lobule, and thalamus.



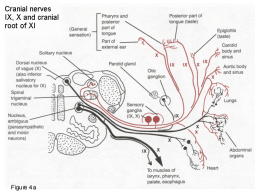


Figure 4a

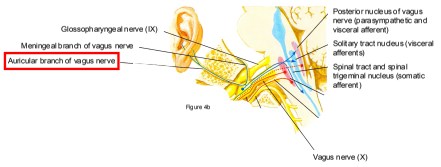


Figure 4b

Discussion

Electrical stimulation of the concha activates the NTS and its known projections.

Specifically: parabrachial nucleus, nucleus accumbens, hypothalamus, and amygdala. Additional activity was found in the insula and paracentral lobule (genital area of the sensory cortex).

Electrical stimulation of the external ear exerts physiological effects comparable to those elicited by invasive stimulation of the main vagus trunk in the neck, specifically against epilepsy, pain and depression.[1-5,15,16,20]

This and other[7] evidence is seemingly inconsistent with the anatomical descriptions claiming that the auricular branch of the vagus nerve projects to the spinal trigeminal nucleus, not to NTS.[8,9] (Figure 4a,b). However, the functional activation of the NTS may not be limited to the classical anatomical projection, for the 2 nuclei are adjacent and, therefore, it is possible that afferent activity to spinal trigeminal nucleus could spread to the NTS. The significant and widespread activation in the brainstem that occurs in response to concha stimulation may be due to the non-physiological nature of the electrical stimulation.

A striking finding was the diametrically opposite response of the hippocampus to concha stimulation versus earlobe stimulation.

That is, concha stimulation strongly *deactivated* hippocampal activity, whereas earlobe stimulation *activated* it. This is consistent with the reported antiepileptic effects of stimulation of the sensory fields of the auricular branch of the vagus nerve.[2] The activation of the nucleus accumbens is consistent with antidepression effects of concha stimulation.[11]

The present finding that the septum is activated by concha stimulation suggests that this is an access route from NTS to hippocampus.[12]

Previous research provided evidence that the vagus nerve conveys vaginal and cervical afference.[13-15,19]

Recent evidence using fMRI showed that the vagina and cervix project to the paracentral lobule, which is the genital region of the sensory cortex.[14] This is consistent with the report that women with "complete" spinal cord injury at and above T10, which would block all known genital spinal afference through the spinal cord, were still able to feel vaginal and cervical stimulation. This observation suggested that the vagus nerves convey vaginal and cervical afferent activity to the brain, and was confirmed by fMRI evidence that the NTS was activated by vaginal and cervical stimulation in these women.[13]

Conclusion

We provide fMRI evidence that the vagus input to the brain is accessible non-invasively from the external ear, specifically the concha.

The pattern of activation and deactivation of brain regions in response to electrical stimulation of the concha provides a rational basis for the reported antiepileptic, antidepressive, and antinociceptive effects of stimulation of the auricular branch of the vagus nerve.

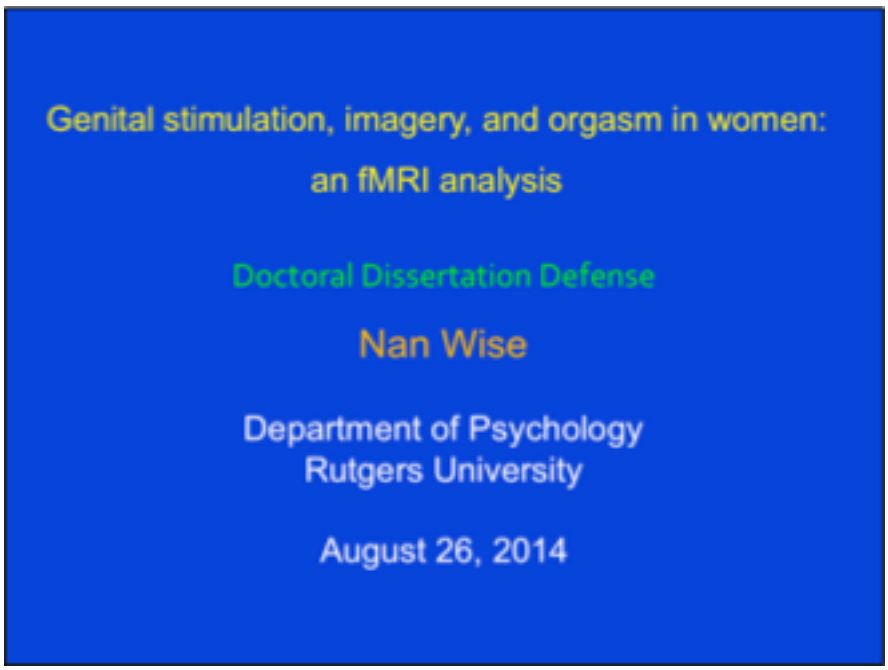
Acknowledgements

Support: Cerbomed GmbH, Erlangen, Germany; and NIH 2R25 GM 060826 (BRK).

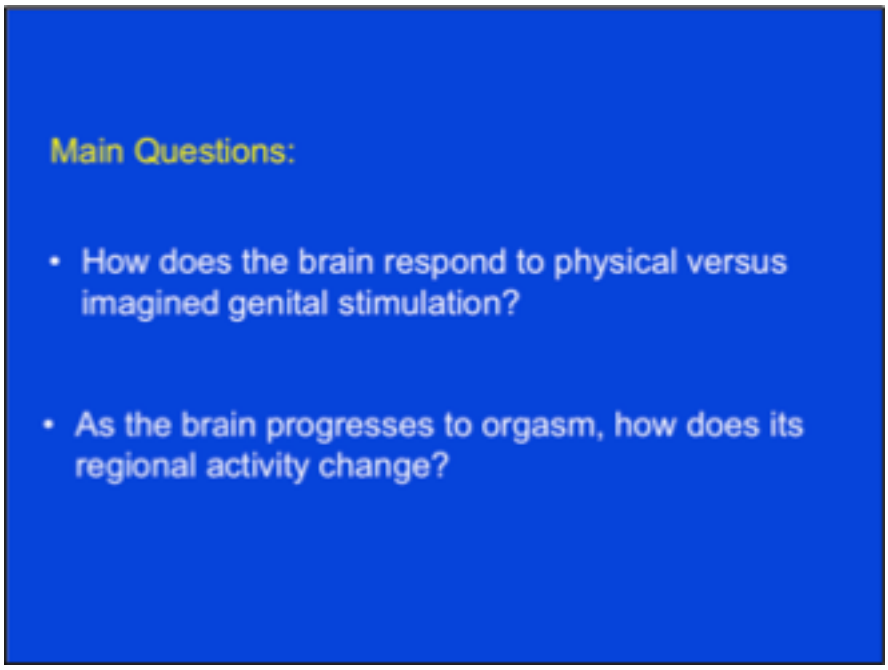
We gratefully acknowledge Wendy Birbano for excellent technical assistance.

References

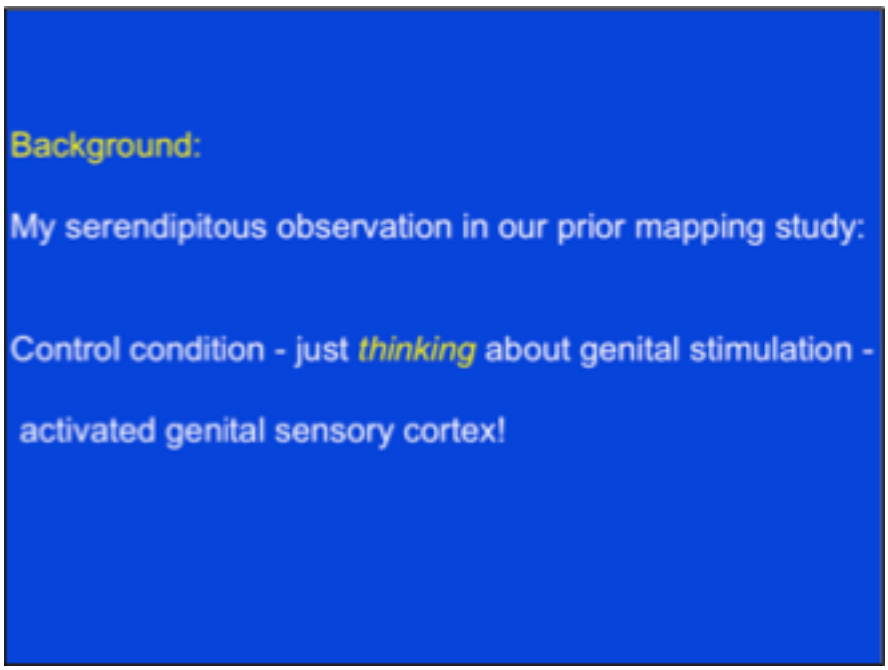
1. Ward H.E. Jr, Nihan P.T., Pollack M., Nahas Z., Anderson B., Kose S., Howland R.H., Goodman W.K., Ballenger J.C. 2008. A pilot study of vagus nerve stimulation (VNS) for treatment-resistant anxiety disorders. Brain Stimul. 1(2):112-21.
2. Stefan H., Kreiselmeyer G., Kerling F., et al. 2012. Transcutaneous vagus nerve stimulation (t-VNS) in pharmacoresistant epilepsies: a proof of concept trial. Epilepsia. 53(7):e115-8.
3. Busch V., Zeman F., Heckel A., Menne F., Ellrich J., Eichhammer P. 2012. The effect of transcutaneous vagus nerve stimulation on pain perception - An experimental study. Brain Stimul. [ahead of print]
4. DeGiorgio C.M., Schachter S.C., Handforth A., et al. 2000. Prospective long-term study of vagus nerve stimulation for the treatment of refractory seizures. Epilepsia. 41(8):1195-200.
5. Corcoran C.P., Cristancho M.A., Barbuto G.H., Thase M.E., O'Reardon J.P. 2011. Effectiveness and safety of vagus nerve stimulation for severe treatment-resistant major depression in clinical practice after FDA approval: outcomes at 1 year. 72(1):1376-82.
6. Peuker E.T., Filler T.J. 2002. The Nerve Supply of the Human Auricle. Clin Anat. 15(1):35-7.
7. Jenkinson M., Bannister P., Brady M., and Smith S. 2002. Improved optimization for the robust and accurate linear registration and motion correction of brain images. NeuroImage 17(2):825-41.
8. Worsley K.J. 2001. Statistical analysis of activation images. Ch 14, in Functional MRI: An Introduction to Methods, eds. P. Jezzard, P.M. Matthews and S.M. Smith. OUP.
9. Nieuwenhuys R, Voogd J, van Huijzen C. 1988. The human central nervous system: a synopsis and atlas. Springer-Verlag.
10. Paxinos G., Huang X.F., Toga A.W. 2000. The Rhesus Monkey Brain in Stereotaxic Coordinates. Academic Press.
11. Kraus T., Hösl K., Kiess O., Schanze A., Kornhuber J., Forster C. 2007. BOLD fMRI deactivation of limbic and temporal brain structures and mood enhancing effect by transcutaneous vagus nerve stimulation. J Neural Transm. 114(11):1485-93.
12. Gogolák G., Stumpf C., Petsche H., Sterc J. 1968. The firing pattern of septal neurons and the form of the hippocampal theta wave.
13. Komisaruk B.R., Whipple B., Crawford A., Grimes S., Liu W.C., Kalnin A., and Mosier K. 2004. Brain activation during vaginocervical self-stimulation and orgasm in women with complete spinal cord injury: fMRI evidence of mediation by the Vagus nerves. Brain Research. 1024:77-88.
14. Komisaruk B.R., Wise N., Frangos E., Liu, W-C, Whipple B., and Brody S. 2011 Women's clitoris, vagina and cervix mapped on the sensory cortex, using fMRI. J Sexual Medicine. 8: 2822-2830.
15. Cueva-Rolon R., Sansone G., Blanca R., Gomez L.E., Beyer C., Whipple B., and Komisaruk B.R. 1996. Vagotomy blocks responses to vaginocervical stimulation after genitospinal neurectomy in rats. Physiology and Behavior. 60:19-24.
16. Dietrich S., Smith J., Scherzinger C., Hofmann-Preiss K., Freitag T., Eisenkolb A., Ringler R. 2008. A novel transcutaneous vagus nerve stimulation leads to brainstem and cerebral activations measured by functional MRI. Biomed Tech (Berl). 53(3):104-11.
17. Ellrich J. 2011. Transcutaneous Vagus Nerve Stimulation. Eur J Neurol Rev. 6(4):254-4.
18. Malcner W. and Randich A. 1984. Role of the right vagal nerve trunk in anticonception. Brain Res. 298:37-47.
19. Moss F., Richard P. 1975. Level of oxytocin release induced by vaginal dilatation (Ferguson reflex) and vaginal stimulation (vago-pituitary reflex) in lactating rats (author's transl.). J Physiol (Paris). 70(3):307-14.
20. Said Yekta S., Vohn R., Ellrich J. 2009. Cerebral activations resulting from virtual dental treatment. Eur J Oral Sci. 117(6):711-9.



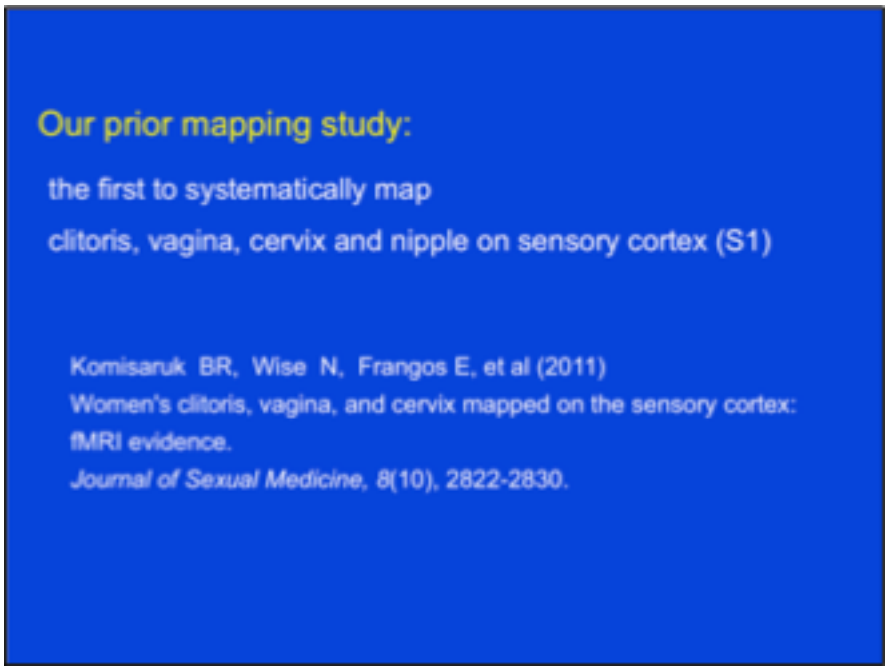
Welcome to my dissertation defense. Thanks for coming.



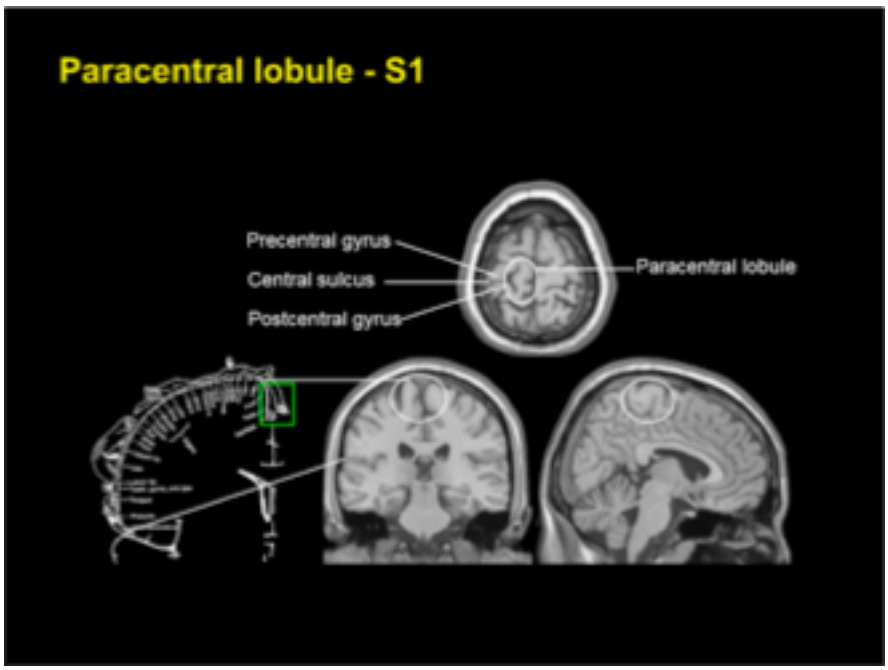
The main questions my dissertation addressed are how does the brain respond to physical versus imagined genital stimulation. And as the brain progresses to orgasm, how does its regional activity change? To address these questions, I conducted two fMRI studies which I will present today.



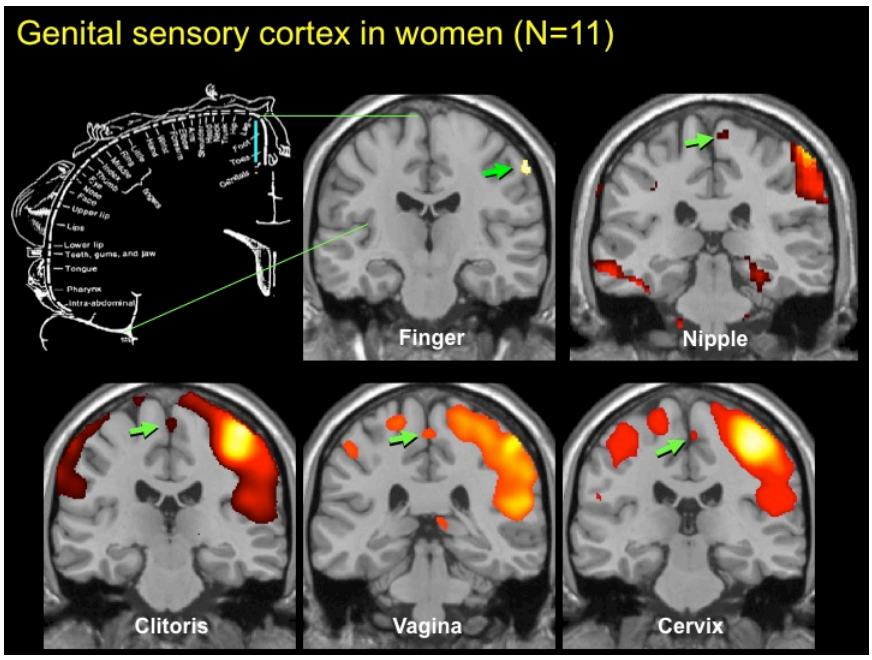
The first study I conducted follows up a serendipitous observation I made in our published mapping study. A control condition in which participants were instructed to just think about genital stimulation resulted in activation of the genital sensory cortex.



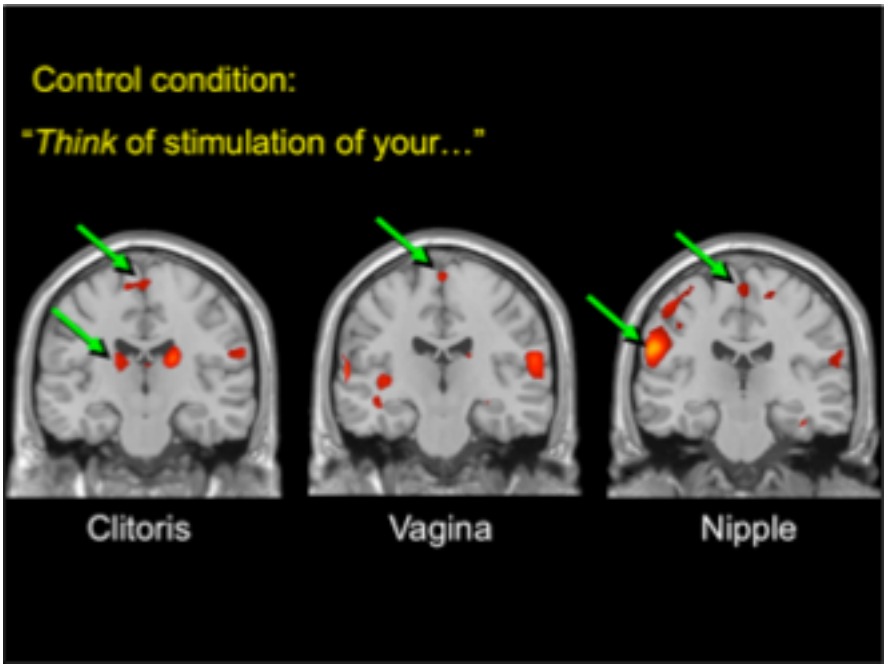
Our prior study was the first to systematically map the clitoris, vagina, cervix, and nipple onto the sensory cortex (S1)



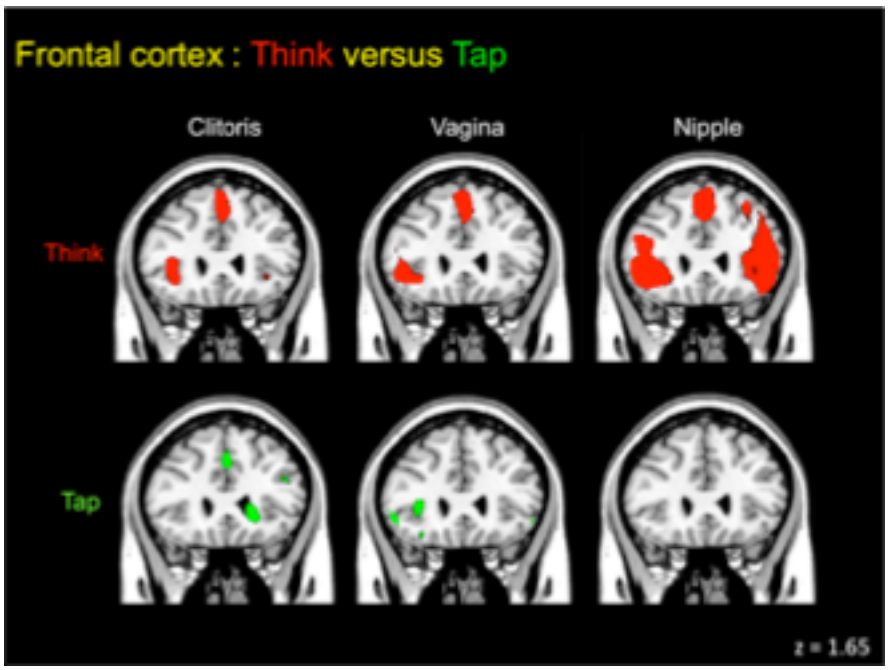
This is the paracentral lobule, located in the sensory cortex. On the lower level is Penfield & Rasmussen's 1950 map of the sensory cortex--the sensory ***homunculus-***- generated by electrical stimulation of the surface of the brain. The sensory *homunculus* is topographically organized along the surface of the cortex with the representation of the foot and penis located midline, in the paracentral lobule, and the leg, pelvis, trunk, arms, hand, face, and mouth extending more laterally. Penfield did not map the FEMALE genital sensory cortex. This omission prompted our study. Furthermore, the overall lack of research regarding the neural correlates of female sexuality motivated me to pursue this line of research. I thought this would have important clinical applications, which I will discuss later.



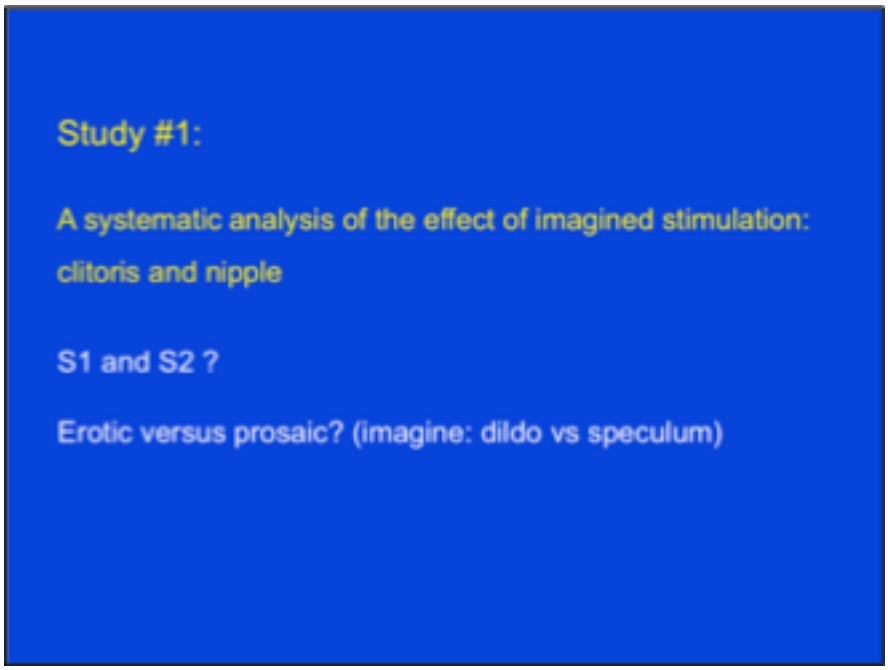
IN our prior study of the genital sensory cortex in women, we also mapped the location of the finger and nipple as reference points. Our results indicate that the clitoris, vagina, and cervix are represented in the paracentral lobule of the sensory cortex, as Penfield found for the penis. In addition to the paracentral activations, you can see lateral sensory cortex activations for arm and hand in the conditions involving self stimulation. Of note: We were surprised to find that in addition to the expected lateral projection to the trunk region, nipple stimulation also activated the GENITAL sensory region (upper right of the slide)



This slide shows results from the control condition of the mapping study. When participants were asked to imagine specific body parts being tapped, without any physical stimulation, this resulted in a surprising observation: just thinking about these body parts being tapped produced brain activations in the paracentral lobule similar to that induced by actual physical stimulation. You can see that the sensory thalamus (the lower arrow on the left) and secondary sensory cortex (lower arrow on the right) were also activated. In other words, when participants were instructed to think about the sensations of their clitoris, vagina, or nipple being tapped, the brain activations looked similar to those from physical genital stimulation.

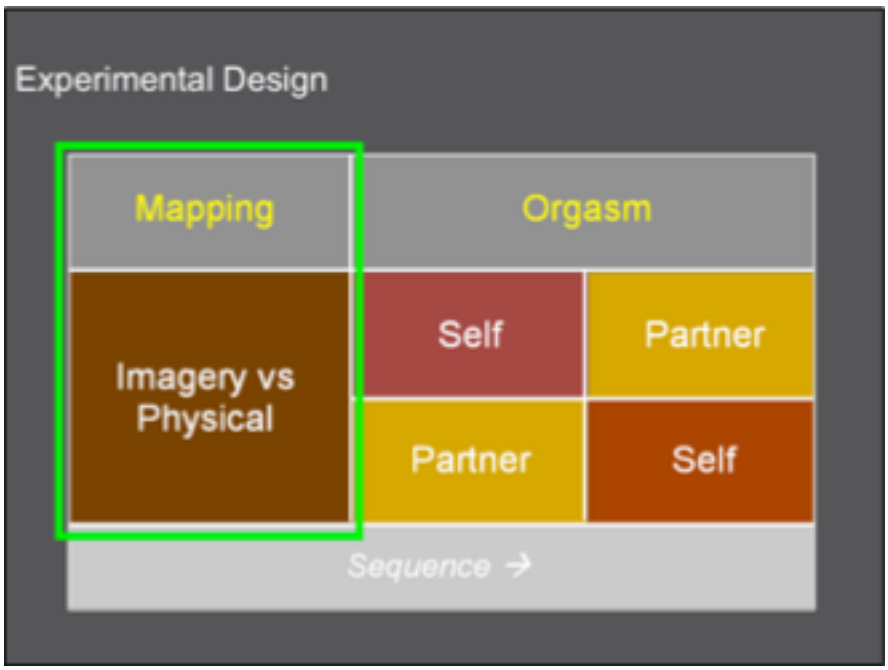


In contrast to the similarity between thinking and physical stimulation in paracentral lobule, there was greater activity in the f*ronta*l regions during the think conditions than the tap conditions. These observations led me to design the first study of my dissertation.

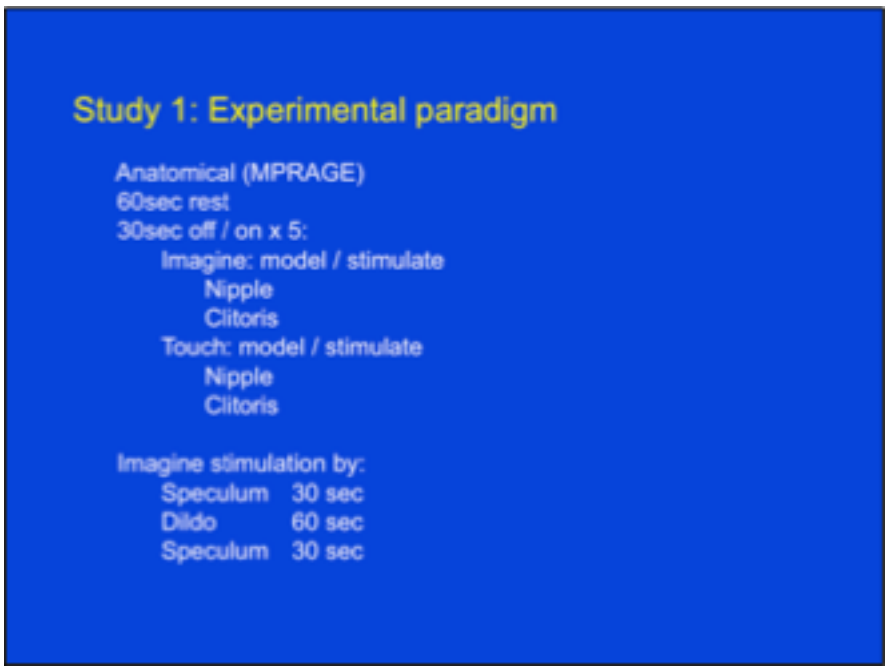


Study one is a systematic analysis of the effect of imagined stimulation. We compared imagined stimulation of the clitoris and nipple with physical stimulation, extending our analysis from the primary sensory cortex (S1) to include the secondary sensory cortex (S2), and other brain regions. We also added a new condition in which we compared two types of imagery—erotic —and prosaic—by comparing imagined dildo stimulation with imagined speculum stimulation.

Our research participants were recruited by word of mouth. They self-identified as easily orgasmic during prescreening. I conducted two open-ended interviews, one pre- scan for personal history collection, and the other, post-scan, for them discuss their experiences in the scanner. During the post-scan interview, they rated the vividness of the imagery conditions and level of sexual arousal during physical and imagery conditions.

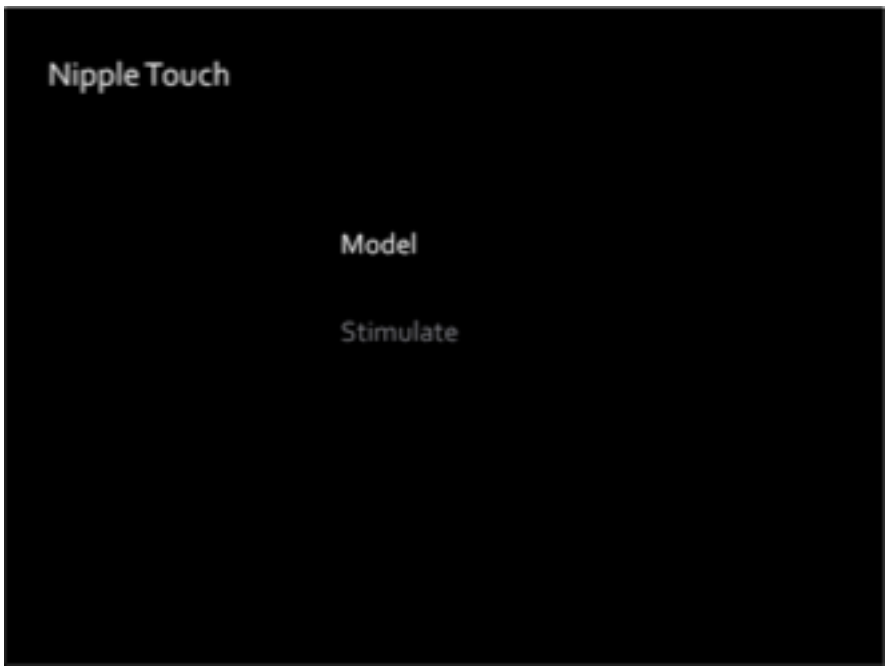


Here is an overview of the design of my two studies, both of which were conducted sequentially, during one continuous scanning session. The data for the imagery vs. physical mapping study (that is study 1, labeled as mapping) were obtained during the first 22 minutes of the scan. The data for study #2 (labeled as orgasm) were obtained during the second part of the same scan.

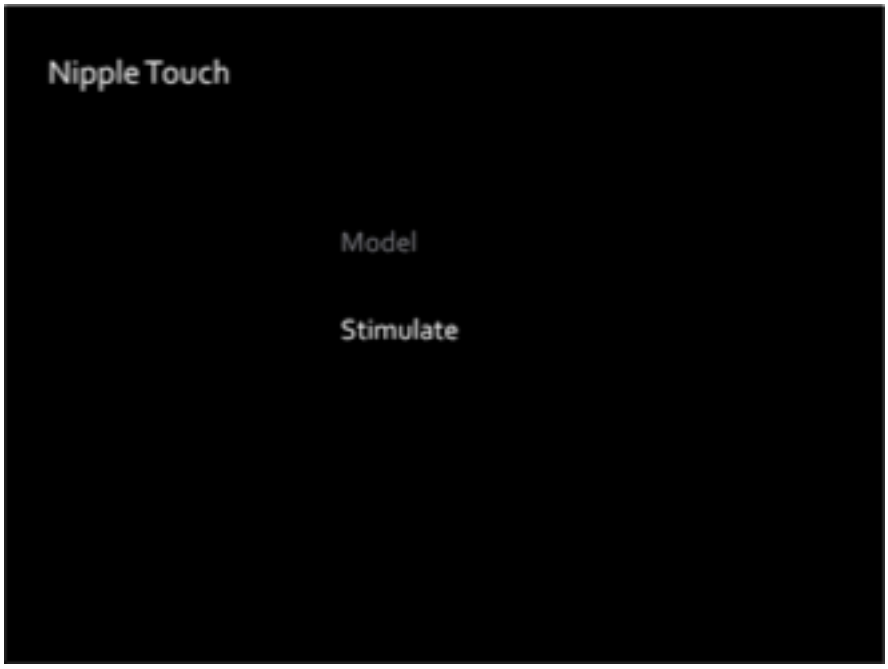


After collection of the anatomical images, the participants rested for 60 s. The conditions followed a conventional box car paradigm of 30 s off and 30s on, 5 times in succession, for a total of 5 minutes. The control condition is labeled as model. I will describe that shortly. The imagery trials followed in separate conditions. First was imagined nipple stimulation, followed by imagined clitoral stimulation. For these conditions, the participants were instructed to think about stimulating *their own* body parts. Then the physical touch conditions followed, with nipple touch first, followed by clitoris touch. The controls"-- for the nipple and clitoris imagined and physical stimulation—which we called "model" –were implemented in order to keep the control and stimulation conditions as similar as possible, except for the unique aspect of the condition of interest.

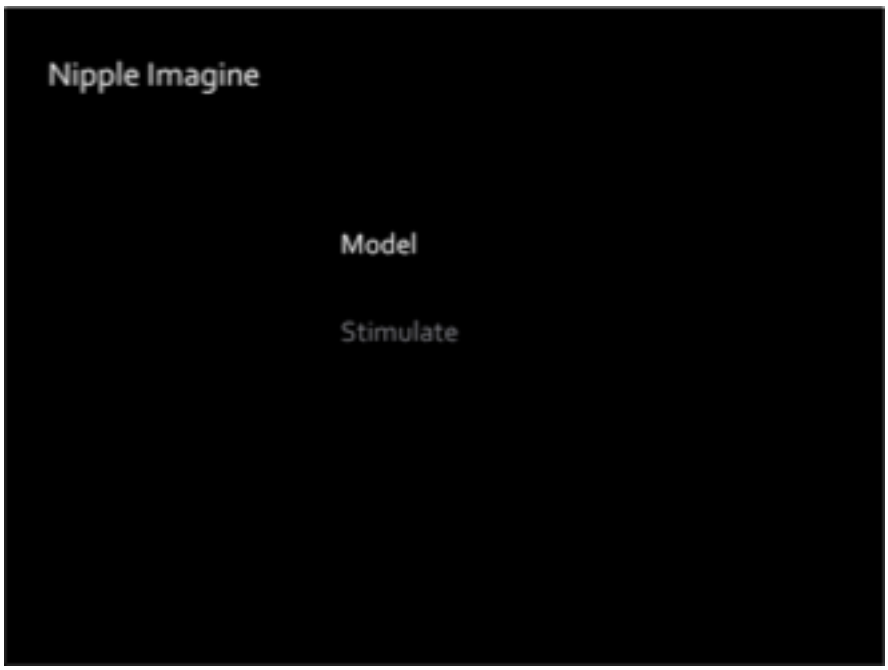
For the final imagery condition, imagined dildo stimulation vs. imagined speculum stimulation, the participants alternated between the two imagery conditions for total of two minutes, and were instructed to imagine *someone else* doing the stimulation.



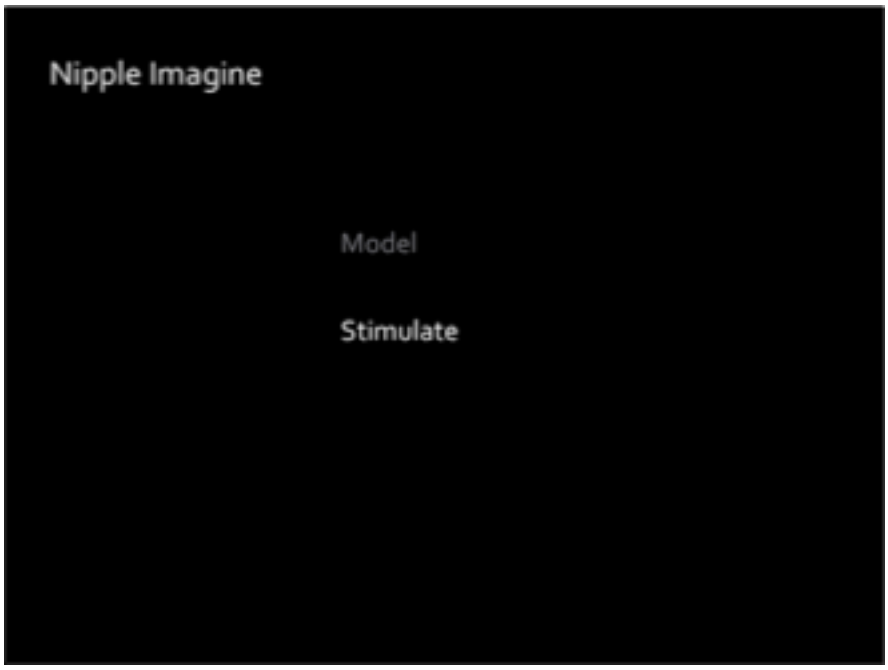
To make the “model” control condition clear, consider the Nipple Touch Stimulation trial. The participant first sees the instruction, “nipple model,” cueing her to make the hand movements that she would do to rhythmically stimulate her nipple without actually touching herself. Thus, the participant moved the fingers of her right hand above her left nipple, fingers touching each other, but not her nipple, for 30s.



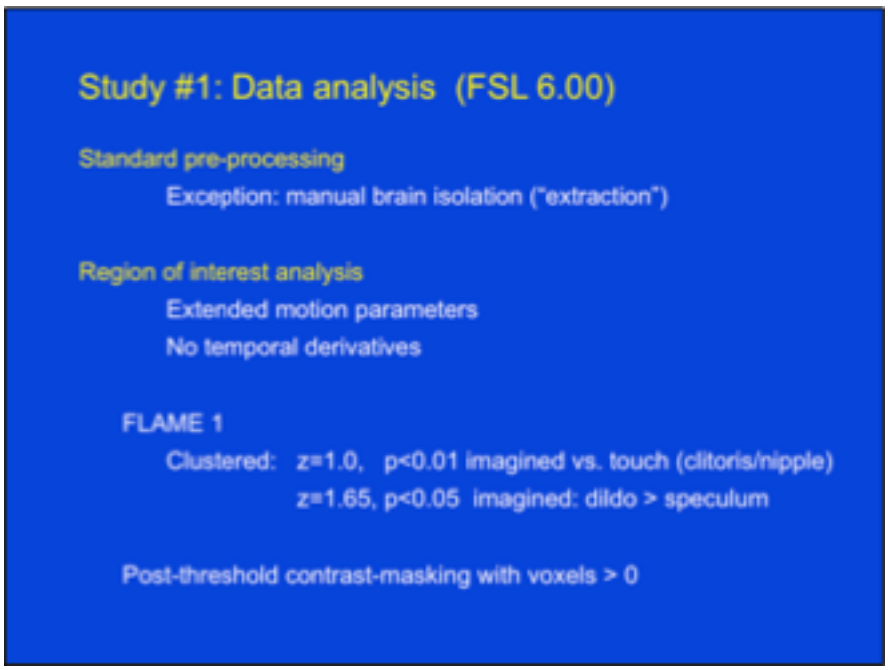
For nipple touch, the participant was then cued to use her right hand to rhythmically stimulate her left nipple. This sequence of nipple “model” and nipple “touch” alternated 5 times for a total of 5 minutes.



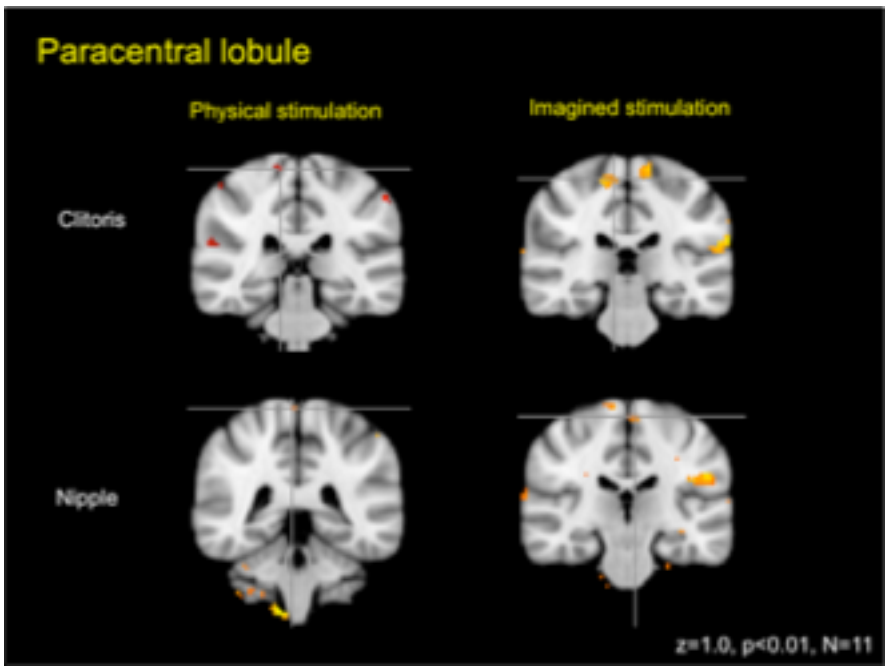
For the nipple **imagine** trial, the “model” control condition was analogous to the model condition for the physical trials, but the participant was instructed to *think* about making the modeling movements, rather than physically execute them.



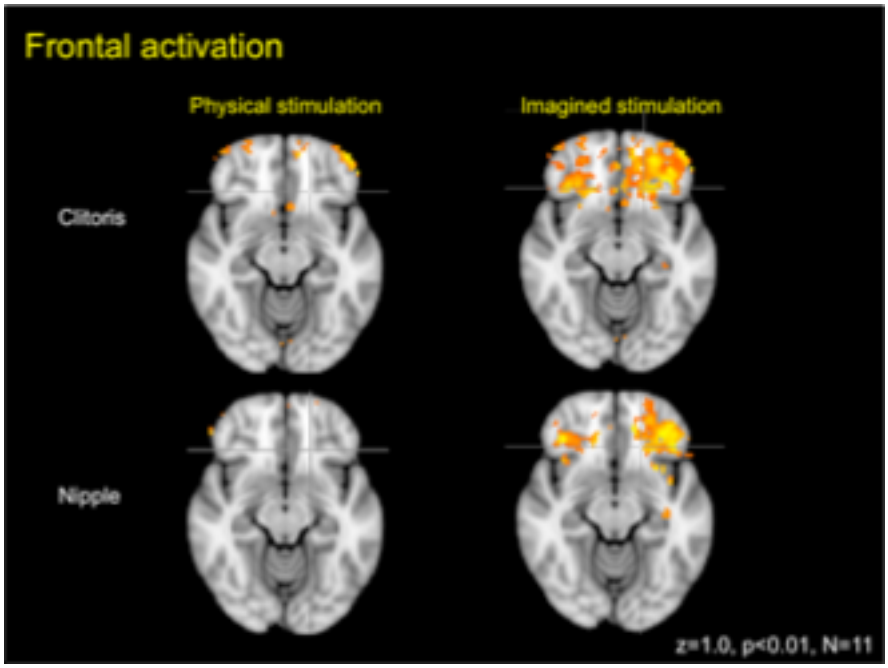
For **nipple** imagine stimulation, the participant sees the instruction, “stimulate,” which cued her to *imagine* rhythmically touching her left nipple with her right hand for 30 s. The same protocol was used for the **clitoris** imagined stimulation and **clitoris** touch conditions.



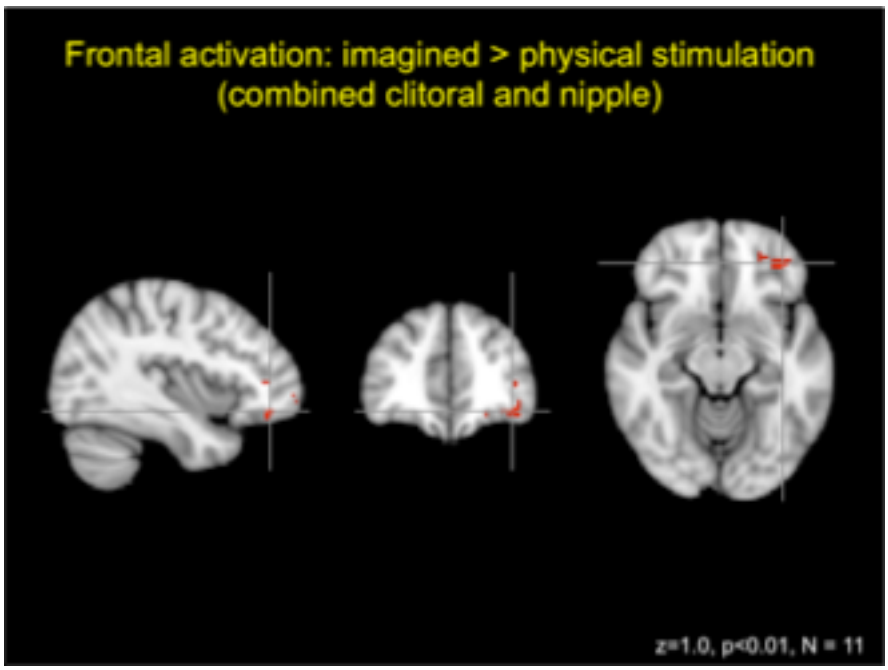
Study 1 data analysis. The data were analyzed with FSL. Because I found lower than expected activity for the physical stimulation conditions, I used preselected regions of interest to increase the power of the analysis, and lowered the threshold for the clitoris and nipple imagined versus physical stimulation data. Contrast-masking post threshold assured that the results reflected only activity above baseline. Rather than go into more detail, I welcome any questions you have about the methods.



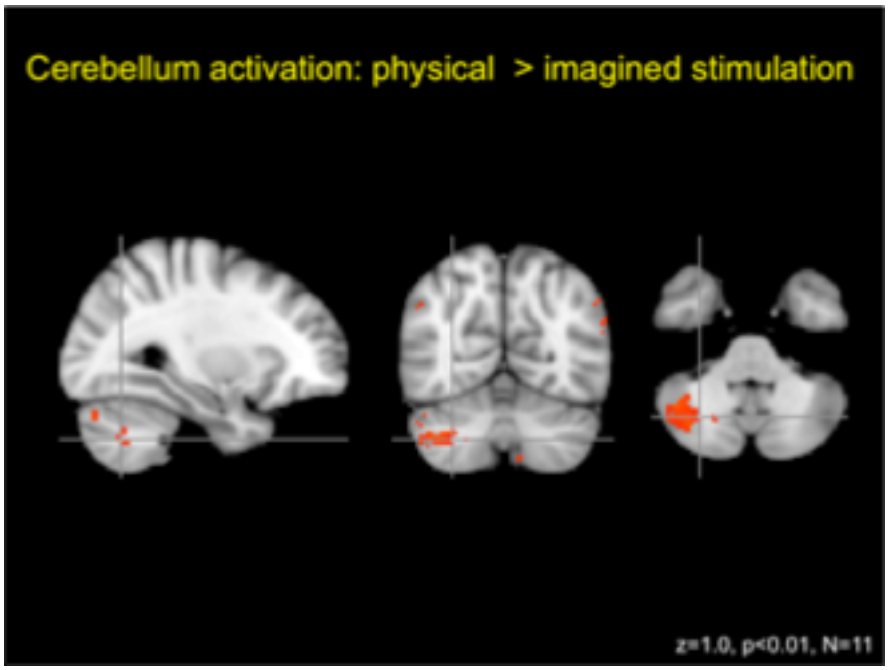
Now for results. The paracentral lobule— the genital sensory cortex– identified by crosshairs--was activated by both physical and imagined stimulation of the clitoris and nipple. When compared statistically, the physical stimulation conditions did not result in greater activation of the genital sensory cortex than the imagined stimulation conditions.



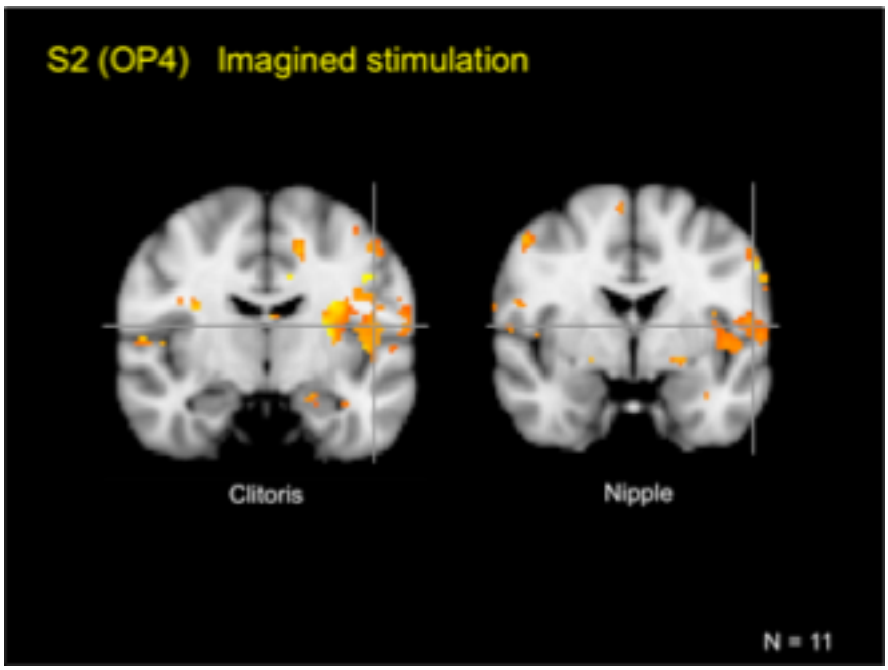
Contrary to the similarity of activation of the paracentral lobule, there was a marked difference between physical and imagery stimulation in the frontal cortex. Physical stimulation of the clitoris and nipple resulted in small regions of activation of the frontal cortex, while imagined stimulation of the clitoris and nipple resulted in greater activation of the orbital frontal cortex and frontal pole



When we combine data from imagined stimulation of clitoris and nipple, and compare that with combined data for physical stimulation of clitoris and nipple, the resulting statistical contrast indicated greater activity of the left orbital frontal cortex and frontal pole in the imagery conditions.

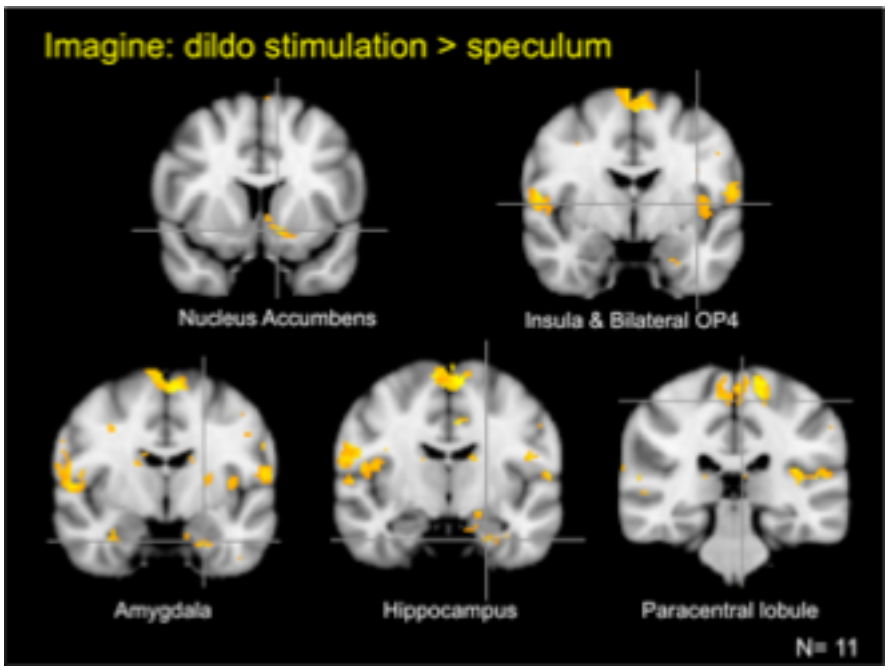


In contrast, in the cerebellum, physical stimulation produced greater activation than the imagined stimulation. In this case, data were combined for the physical stimulation conditions (clitoris and nipple) and statistically compared with data combined for the imagined stimulation conditions.

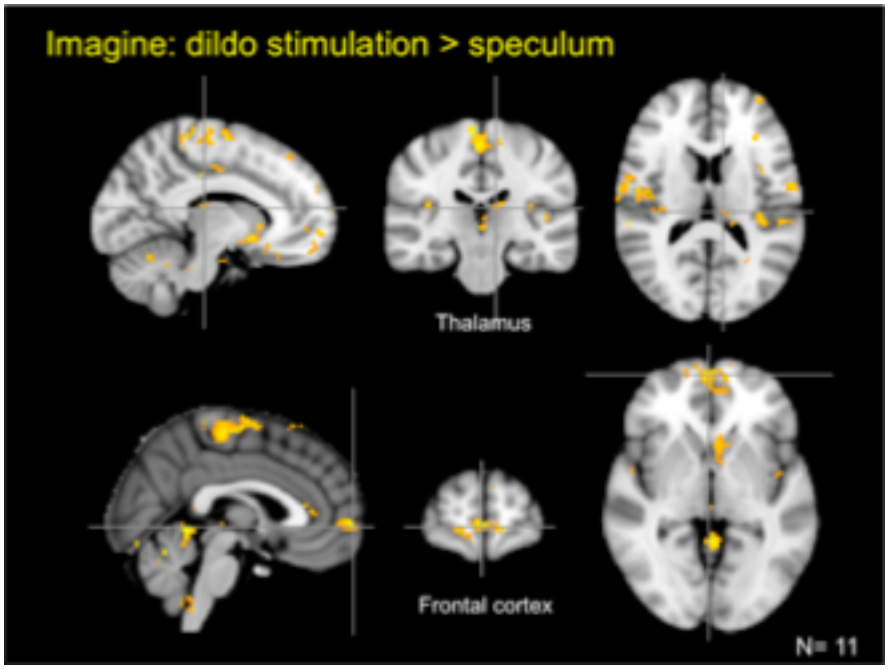


In the case of S2—the secondary sensory cortex, I will briefly discuss how it differs from S1—the primary sensory cortex. For one thing, far less is known about S2. It appears to play a role is somatosensory attention, and participates in the evaluation of sensation. The area of S2 termed OP4 has been shown to contain a somatotopically organized body map, similar to S1, with less detail, but more affected by attention. As shown on the slide, area OP4 of S2 is activated by imagined stimulation of the clitoris and nipple.

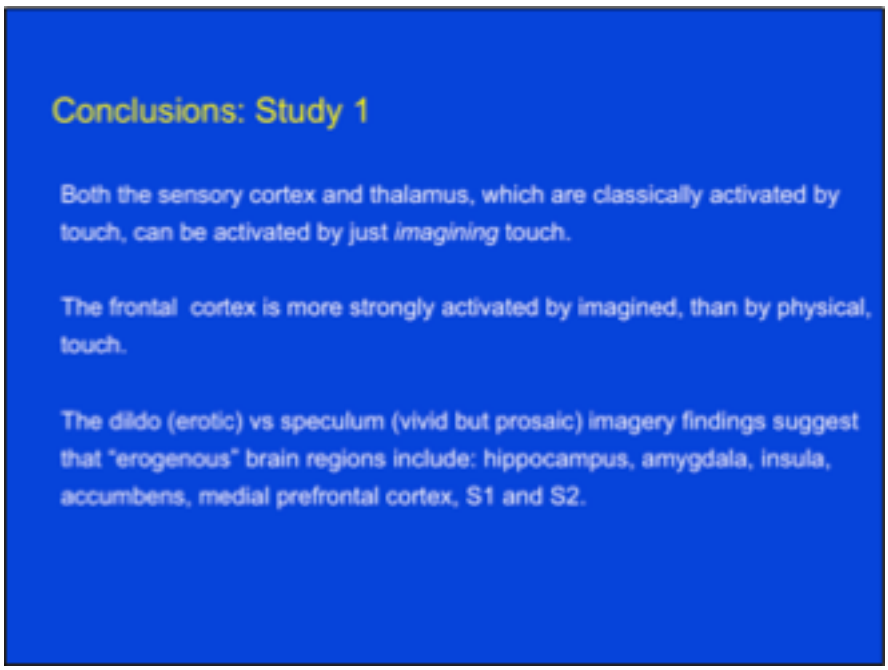
In the second part of study 1, we compared imagined dildo (erotic) stimulation with imagined speculum (prosaic) stimulation.



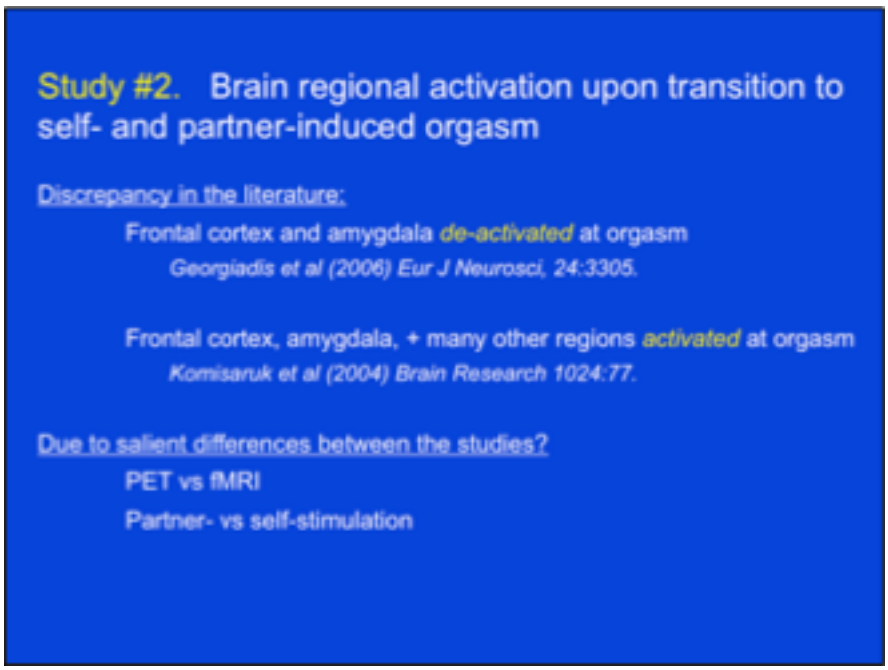
These are the results for imagined dildo stimulation activation greater than imagine speculum stimulation. On the top left, we see activity in the accumbens—a region associated with the reward system. On the top right, we see bilateral S 2, and left insula—regions involved in sensory integration. On the bottom row, from left to right, we have activity in two regions of the limbic system (the amygdala and hippocampus)-- and finally at the far right, we have activation of the genital sensory cortex. There were no brain regions that we more activated by imagined speculum stimulation than imagined dildo stimulation.



Additional results for the dildo imagery greater than speculum imagery condition include the sensory thalamus (top) and medial prefrontal cortex (bottom).

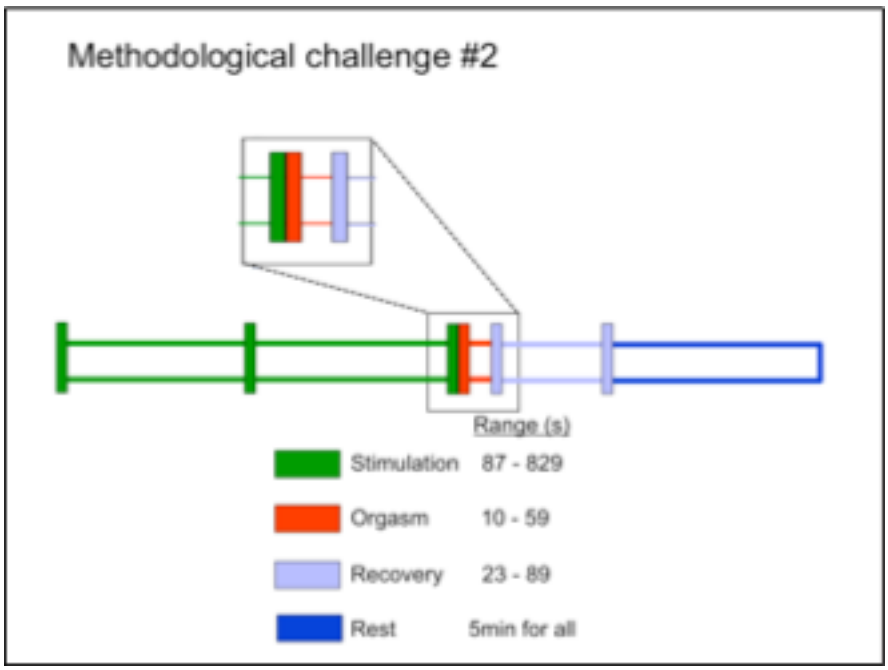


We conclude that both the sensory cortex and thalamus, regions which were believed to be activated only by physical, mechanic touch, can also be activated by just imagining touch. We also conclude that the frontal cortex is more strongly activated by imagined, than physical touch. The results of the imagined dildo versus speculum suggest that brain regions that contribute erogenous experience include the hippocampus, amygdala, insula, accumbens, medial prefrontal cortex, and the sensory cortices.

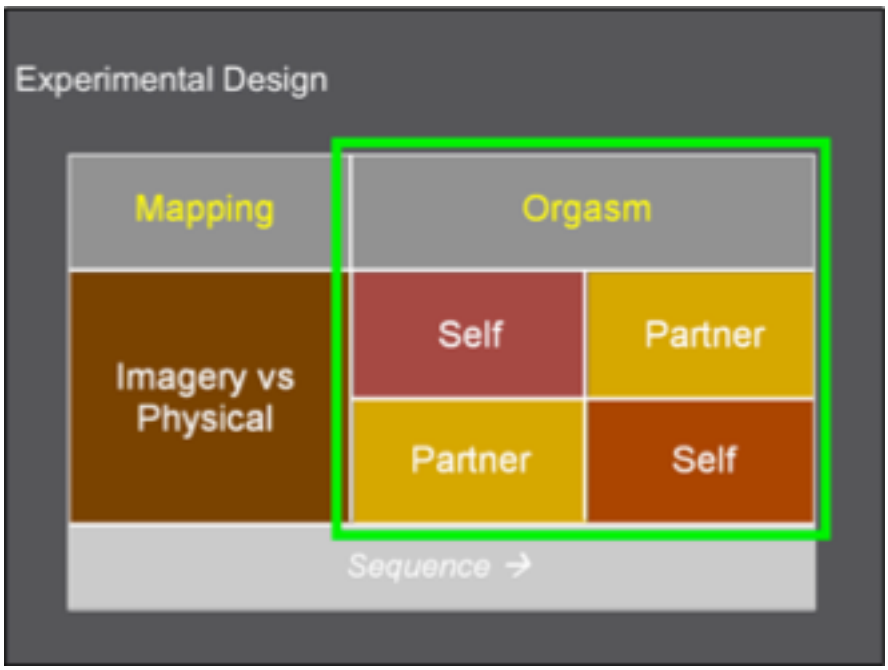


Study 2: Brain regional activation upon transition to self- and partner-induced orgasm addressed a major discrepancy in the literature regarding what happens in the frontal cortex and amygdala at orgasm. The Georgiadis lab—using PET– have reported that these regions are *deac3vated* at orgasm, while we--the Komisaruk lab—using fMRI– have reported that the frontal cortex, amygdala, and many other regions are **activated** at orgasm. Beside the different methods used, PET vs. fMRI, another important difference is that the Georgiadis lab used partner stimulation, while our lab used self- stimulation. In an attempt to reconcile this discrepancy, this study compared self- stimulation-induced orgasm with partner-stimulation induced orgasm.

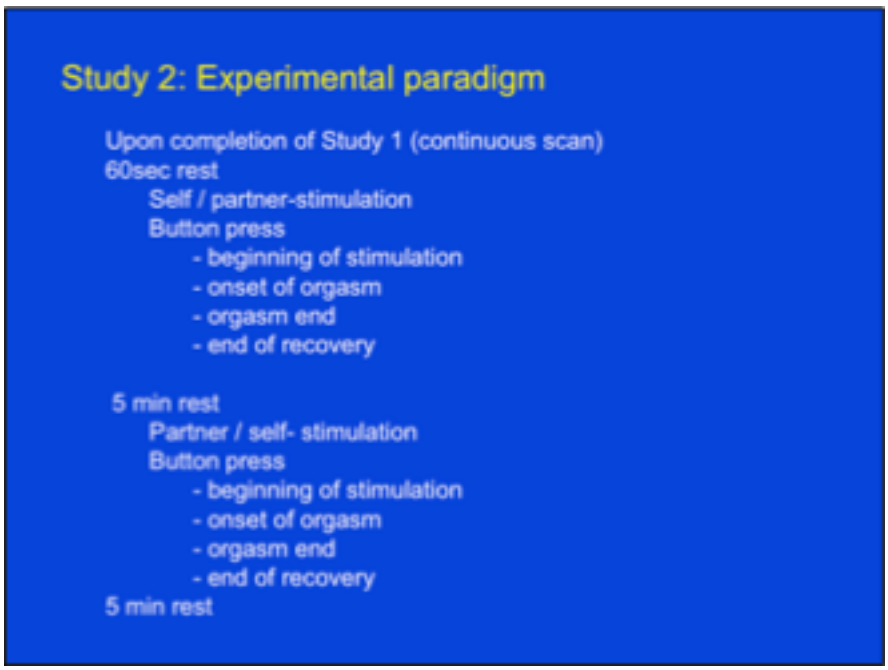
We had two methodological challenges in performing the study. Challenge #1 is artifact caused by head movement which is the biggest problem faced by fMRI studies. Head movement poses a challenge to both spatial and temporal resolution. A shift in head position as small 2mm—can cause reduction in the signal to noise ratio. In a typical orgasm scan in the past, we had 6- 12 mm of movement. We had developed an effective head restraint system (featured on the right) for our old scanner, but had to reinvent it for the new scanner at RUBIC. To protect his confidentiality, we disguised the gentleman on the left, who is sporting the new version. Notice that we had to cut the blue plastic frame, around which we mold the thermoplastic material, in order to fit into the Trio scanner, and added a rigid foam cervical collar, extending up to the back of the head to stabilize the head. For my study, we managed to reduce mean head movement down to a maximum of only 1.3 mm, which allows for effective statistical motion correction.



The second big challenge for orgasm studies is variability in the duration of the stimulation, orgasm, and recovery periods. As shown at the bottom of the slide, the duration of stimulation-- that is the latency to orgasm-- ranged from 87- 829 s, while the duration of orgasm ranged from 10- 59 s. The recovery period—or the time it took for participants to be “over” their orgasm-- ranged from 23 to 89 s. I dealt with this challenge by sampling, across participants, equivalent time points reflecting comparable phases in the stimulation, orgasm, and recovery periods. For stimulation (referring to the green bars), 10 s intervals are sampled at the beginning, middle, and end of stimulation, regardless of the individual latency to orgasm. For orgasm, (the red bar), an interval of 10 s is sampled at orgasm onset. For recovery (the purple bars), 10 s intervals are sampled at the beginning, and end of recovery. At the very top of the slide, you see a magnified representation of the “going over into orgasm” transition, with the green bar representing the last 10 s of stimulation immediately prior to orgasm onset, and the red bar representing the first 10 s of orgasm. The purple bar represents the first 10 s of recovery, immediately after the end of orgasm.



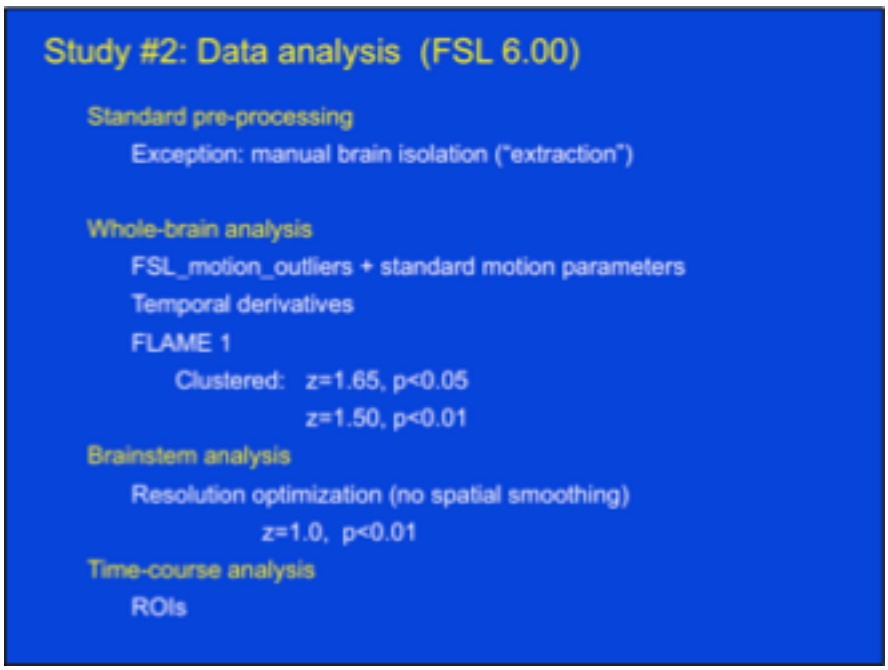
Here is the overall schema of study 2: The plan was to counterbalance the order of self-induced and partner- induced orgasm sequences, such that half of the participants would self-stimulate to orgasm first, before the partner-induced orgasm-- and the other half of participants, vice versa. The participants for study 2, N= 10, were from the same group as study 1, excluding those who were not able to experience orgasm. All participants whose data were used confirmed in the post-scan interview that they had, in fact, experienced orgasms as indicated.



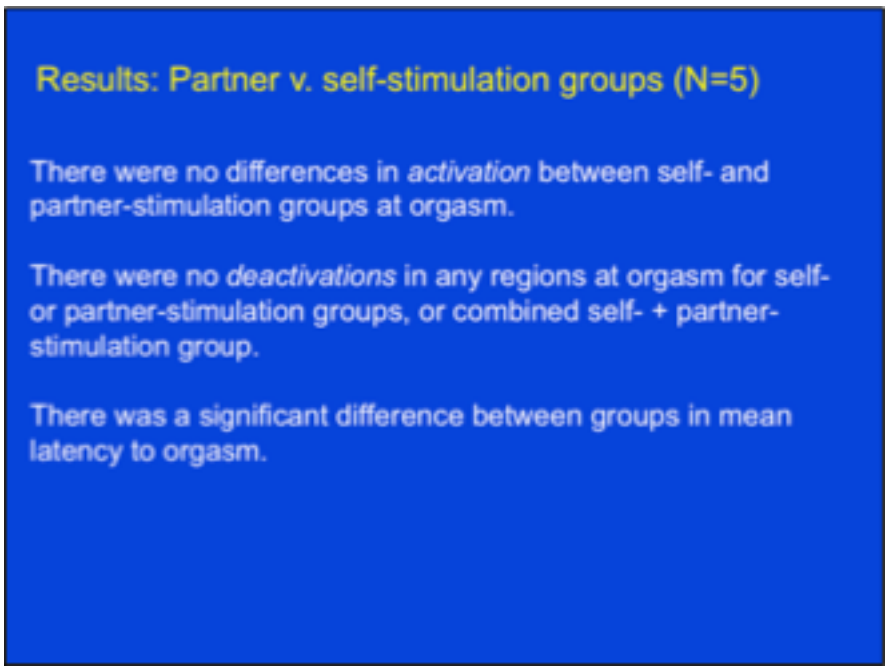
Study 2 started after completion of study 1, and began with 60 s rest. Participants were pre-assigned to one of two groups. The self-stimulation- first group attempted the genital self-stimulation-induced orgasm first, pressing the button consecutive times to indicate when she started stimulation, when orgasm began and ended, and finally, to indicate that she was recovered.

Following five minutes of rest for the participant, the partner stimulation protocol began. Her partner was instructed, via earphones, to begin stimulation. The participant followed the same protocol for indicating, by button press, when stimulation began, when orgasm began and ended, and to indicate she was recovered. In order to counterbalance the sequence, the protocol for the partner-stimulation-first group was the reverse. After completion of both orgasm sequences, the participants rested in the scanner for 5 minutes before the scanning ended.

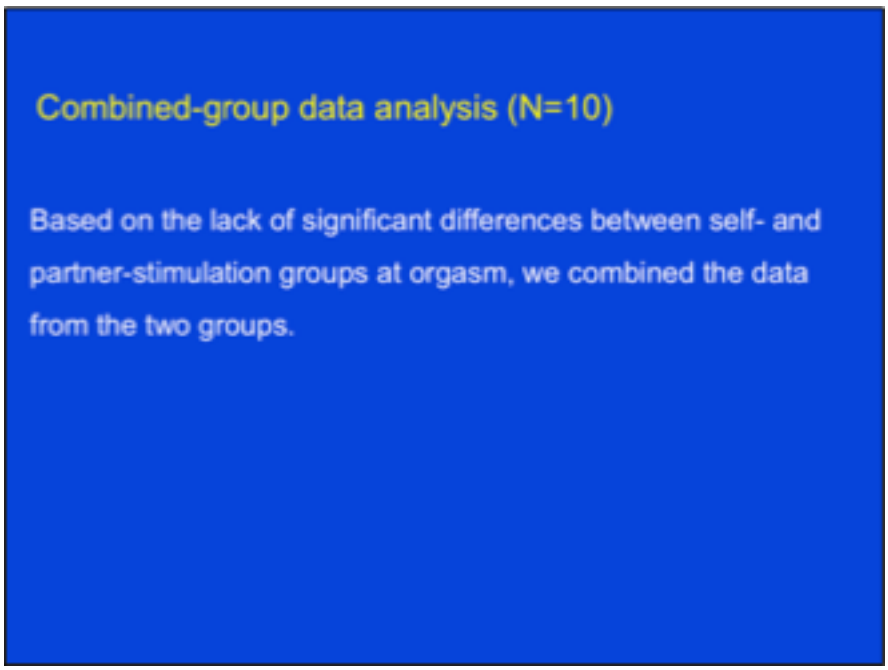
As some participants were unable to experience orgasm during the partner-stimulation sequence, we were unable to counterbalance symmetrically. This prompted the decision to use only orgasms experienced as the first in a scanning session—leaving us with five induced by partner stimulation, and five by self stimulation-- so that we wouldn't have order effects confounding the data.



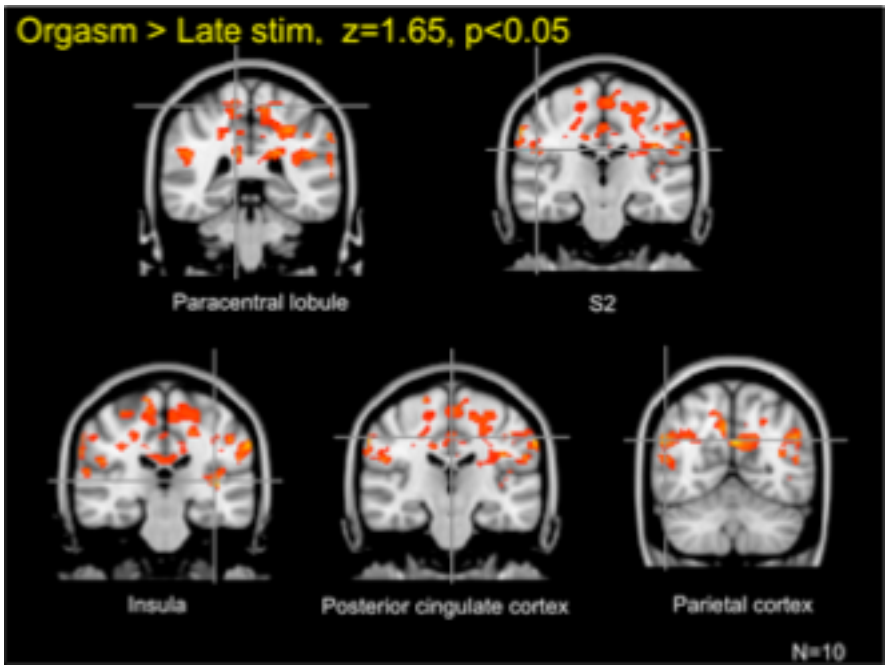
Again, the data were analyzed with FSL. Of special note is that in addition to limiting head movement with our restraint system, FSL-motion-outliers was used in conjunction with standard motion parameters for motion correction. A whole brain analysis was done, as well as an region of interest analysis of the lower brainstem. A time course analysis of the going-over- to orgasm period was also preformed. Again, if you have any questions about methods, feel free to ask.



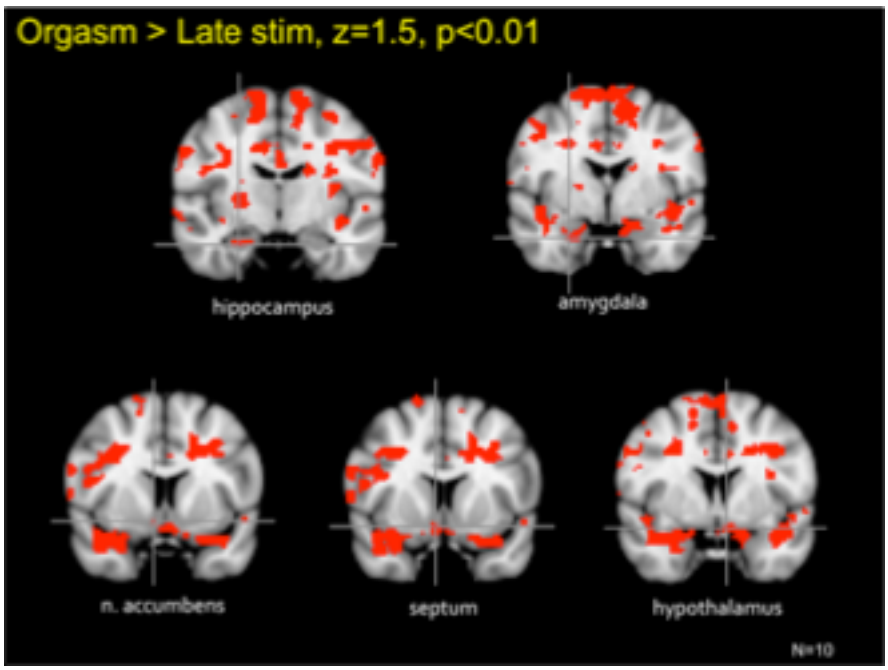
The results of the partner versus self-stimulation group analysis indicated that there were no differences in activation between self and partner stimulation groups at orgasm. Furthermore, there were no deactivations in any regions at orgasm for the self-or partner stimulation group, or when we combined the data from the self and partner groups. There was a significant difference between groups in mean latency to orgasm--with the self stimulation group averaging 165 s of stimulation before orgasm onset, while the partner group averaged 476 s. This contributed to differences between groups during stimulation.



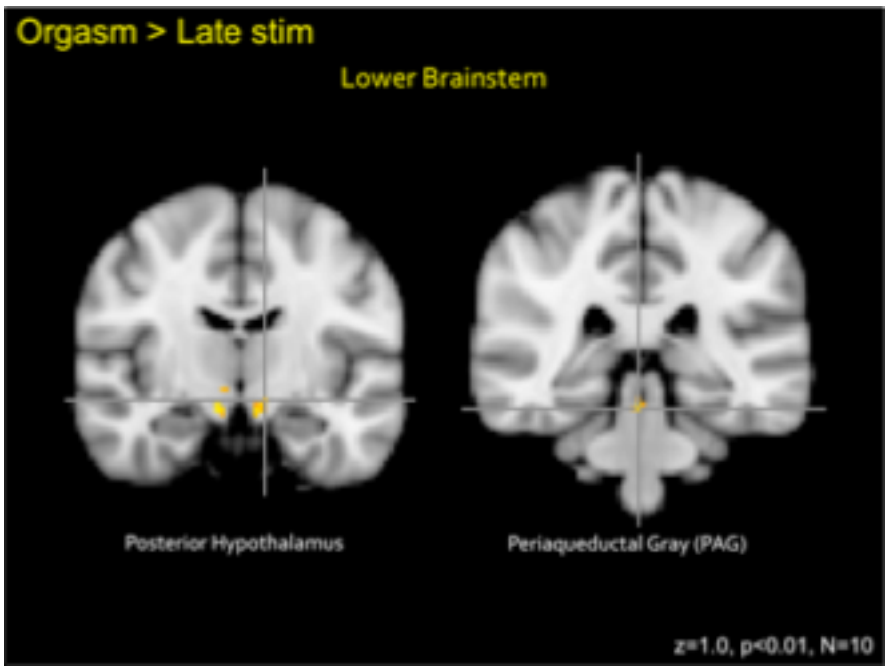
Based on the lack of significant group differences between self- and partner-stimulation groups at orgasm, we combined the data from both groups. I will now present results from the combined group analysis.



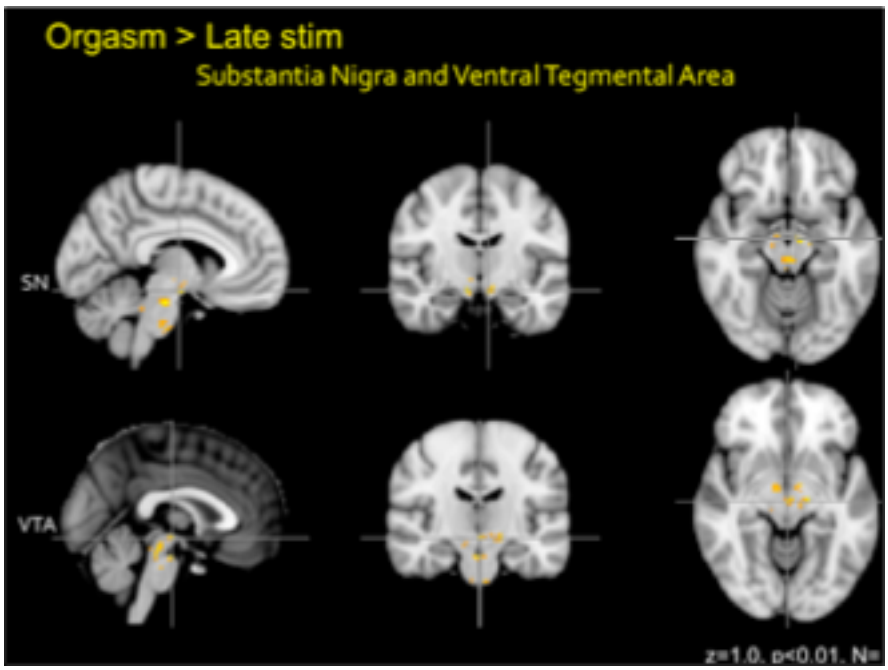
When we look at the going over to orgasm period (that is, the first 10 s of orgasm greater than the 10 s immediately preceding the orgasm) from the vantage of the threshold, z = 1.65, we see activations of sensory regions including the genital sensory cortex (the paracentral lobule) and S2 (top row)-- and sensory integration regions, the insula, posterior cingulate, and parietal cortex (bottom row). From this view, the transition-to-orgasm looks like a major sensory-integration event.



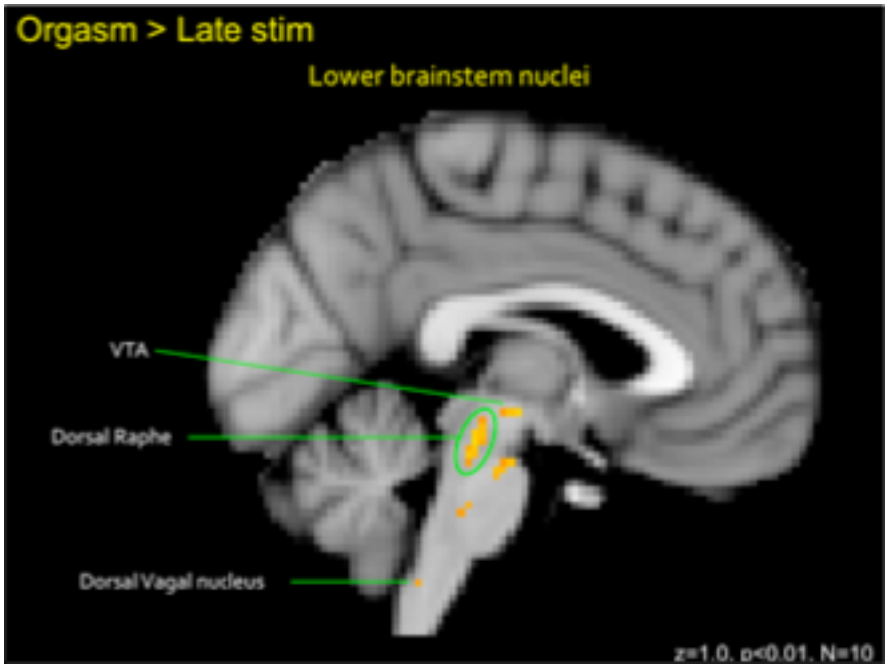
When we drop the threshold just a bit—from a z of 1.65 to 1.5—we see activity in limbic regions such as the hippocampus and amygdala (top row), and reward regions including the accumbens and septum-- and also the anterior hypothalamus (bottom row), where the neurons that secrete oxytocin at orgasm are located.



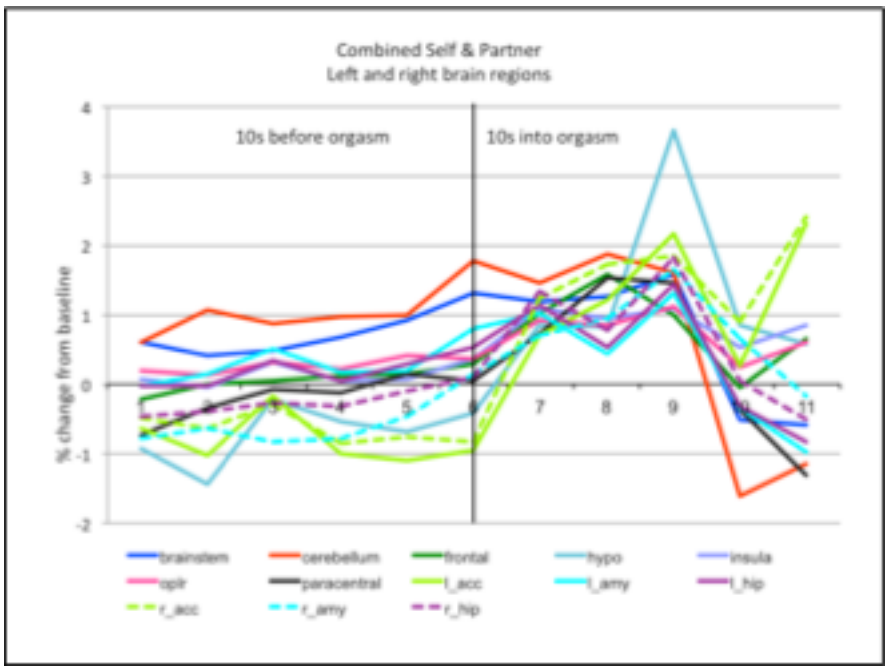
When we see this same transition period, from the perspective of the lower brainstem, we see activation of the posterior hypothalamus that controls the sympathetic division of the autonomic nervous system; sympathetic activation is the predominant autonomic tone at orgasm. The periaqueductal gray, which plays a key role in endogenous analgesia, is also activated. This activation could account for the marked reduction in pain sensitivity that Beverly Whipple, who is sitting in the audience, and Barry, previously reported to occur at orgasm. That finding was Beverly Whipple's doctoral dissertation, which she did here, with Barry.



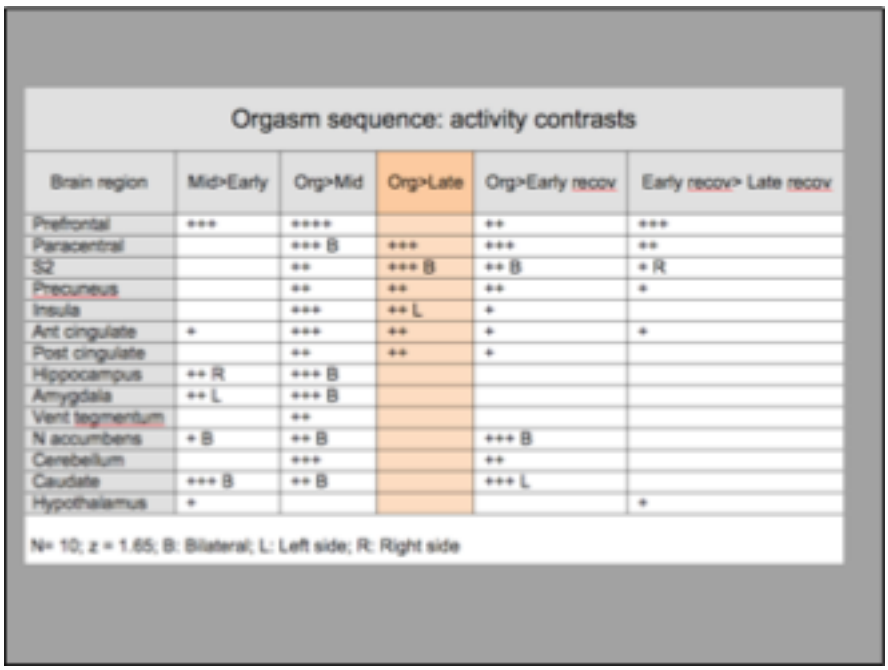
More brainstem regions that are activated in the transition to orgasm include the substantia nigra and ventral tegmentum, which are components of the meso-cortico- limbic dopamine system, involved in pleasure and reward. The ventral tegmental area is the source of dopamine neurons that project to the nucleus accumbens, which was shown in a previous slide to be activated at orgasm.



Again we see activation of the ventral tegmental area on the top, and below that, the dorsal raphe nucleus, another component of the endogenous analgesia system. On the bottom, we see activation in the region of the dorsal vagal nucleus —suggesting that the parasympathetic component of the autonomic nervous system is also activated at orgasm.



In contrast to the analyses we just discussed, comparing the 10 s before and after orgasm, we also performed a time course analysis, breaking the transition period down into 2 second intervals. While an analysis of specific regional differences is premature, the results of this time course study show an overall trend for different brain regions to become activated, leading up to orgasm, and during orgasm, in a variety of patterns. We are continuing this type of analysis, using a longer time frame, and applying effective connectivity methods with Steve and Catherine Hanson's IMaGES program.

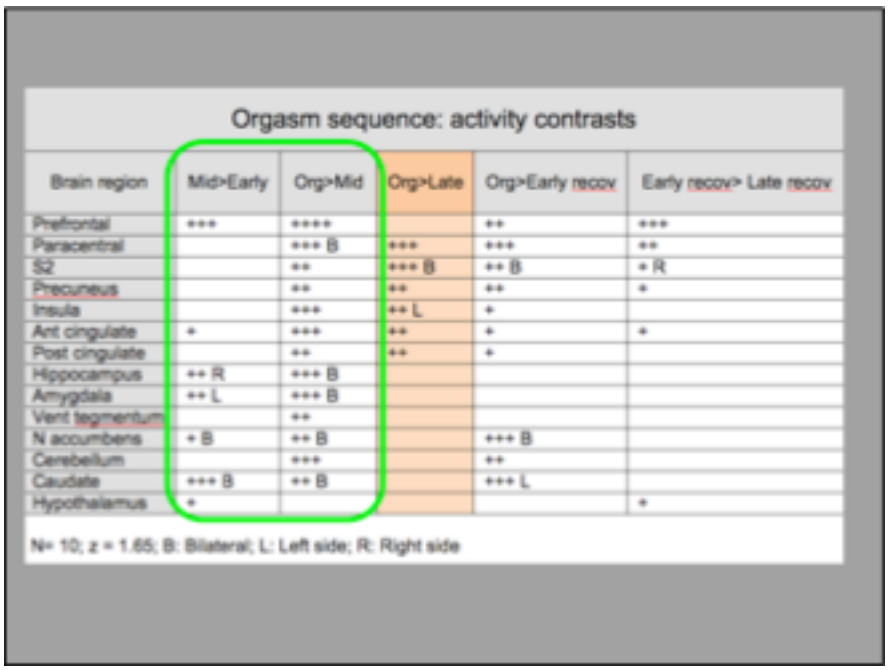


Orgasm sequence: activity contrasts

Brain region	Mid>Early	Org>Mid	Org>Late	Org>Early recov	Early recov> Late recov
Prefrontal	+++	++++		++	+++
Paracentral		+++ B	+++	+++	++
S2		++	+++ B	++ B	+ R
Precuneus		++	++	++	+
Insula		+++	++ L	+	
Ant cingulate	+	+++	++	+	+
Post cingulate		++	++	+	
Hippocampus	++ R	+++ B			
Amygdala	++ L	+++ B			
Vent tegmentum		++			
N accumbens	+ B	++ B		+++ B	
Cerebellum		+++		++	
Caudate	+++ B	++ B		+++ L	
Hypothalamus	+				+

N= 10; z = 1.65; B: Bilateral; L: Left side; R: Right side

Here is a table summarizing the results from other time points in the sequence of stimulation, orgasm and recovery. The grey column on the far left lists the brain regions. From left to right, each column summarizes the results of different contrasts: activity greater in mid stimulation than early stimulation -- activity greater at orgasm than mid stimulation--activity that is greater at orgasm than late stimulation (which is the column in orange)-- activity greater at orgasm than early recovery--and finally, activity greater at early recovery than late recovery. The plus marks indicate the relative degree of activity. The blank spaces mean that there is no significant difference between the two conditions compared in the column. But it is important to recognize that the lack of significant difference, in some cases, reflects comparably high levels of activity.

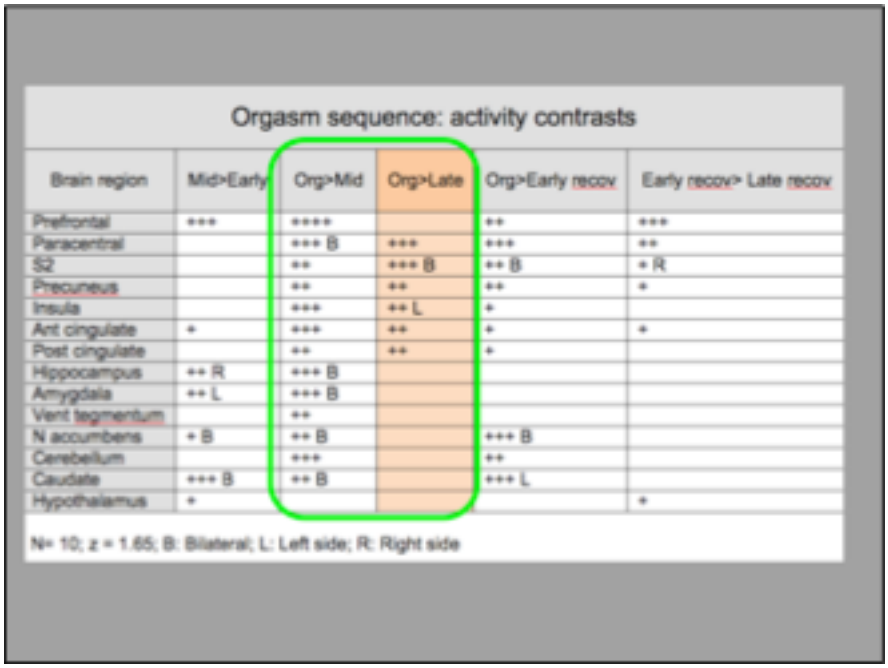


Orgasm sequence: activity contrasts

Brain region	Mid>Early	Org>Mid	Org>Late	Org>Early recov	Early recov> Late recov
Prefrontal	+++	++++		++	+++
Paracentral		+++ B	+++	+++	++
S2		++	+++ B	++ B	+ R
Precuneus		++	++	++	+
Insula		+++	++ L	+	
Ant cingulate	+	+++	++	+	+
Post cingulate		++	++	+	
Hippocampus	++ R	+++ B			
Amygdala	++ L	+++ B			
Vent tegmentum		++			
N accumbens	+ B	++ B		+++ B	
Cerebellum		+++		++	
Caudate	+++ B	++ B		+++ L	
Hypothalamus	+				+

N= 10; z = 1.65; B: Bilateral; L: Left side; R: Right side

The activity in the second column is greater than that in the first column, indication an overall increase in activity at orgasm.

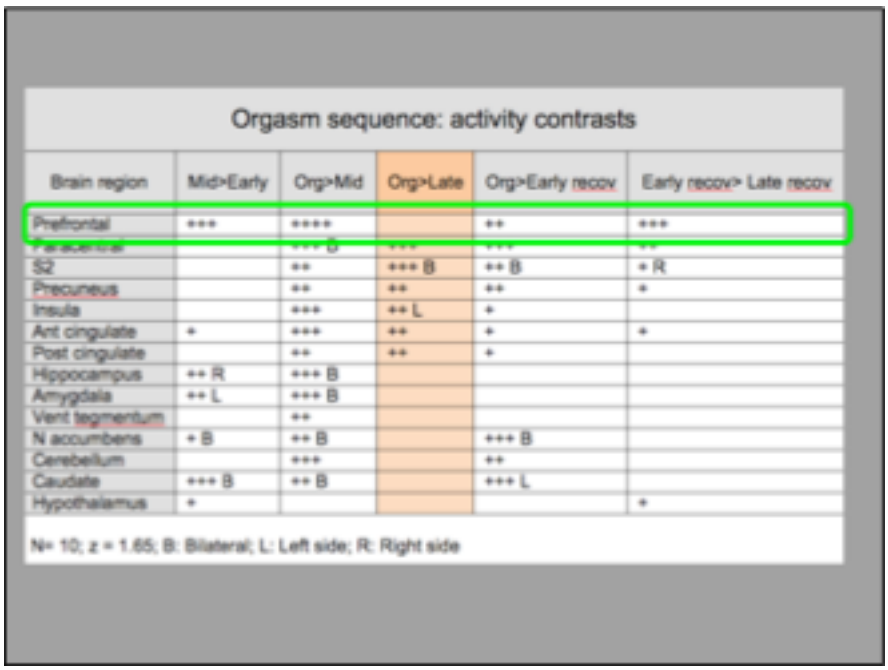


Orgasm sequence: activity contrasts

Brain region	Mid>Early	Org>Mid	Org>Late	Org>Early recov	Early recov> Late recov
Prefrontal	+++	++++		++	+++
Paracentral		+++ B	+++	+++	++
S2		++	+++ B	++ B	+ R
Precuneus		++	++	++	+
Insula		+++	++ L	+	
Ant cingulate	+	+++	++	+	+
Post cingulate		++	++	+	
Hippocampus	++ R	+++ B			
Amygdala	++ L	+++ B			
Vent tegmentum		++			
N accumbens	+ B	++ B		+++ B	
Cerebellum		+++		++	
Caudate	+++ B	++ B		+++ L	
Hypothalamus	+				+

N= 10; z = 1.65; B: Bilateral; L: Left side; R: Right side

Comparison between orgasm and mid stimulation (left column) shows an overall dramatic increase in activity at orgasm. The column on the right emphasizes those brain regions that are particularly, strongly activated in the brief period of transition going over into orgasm.

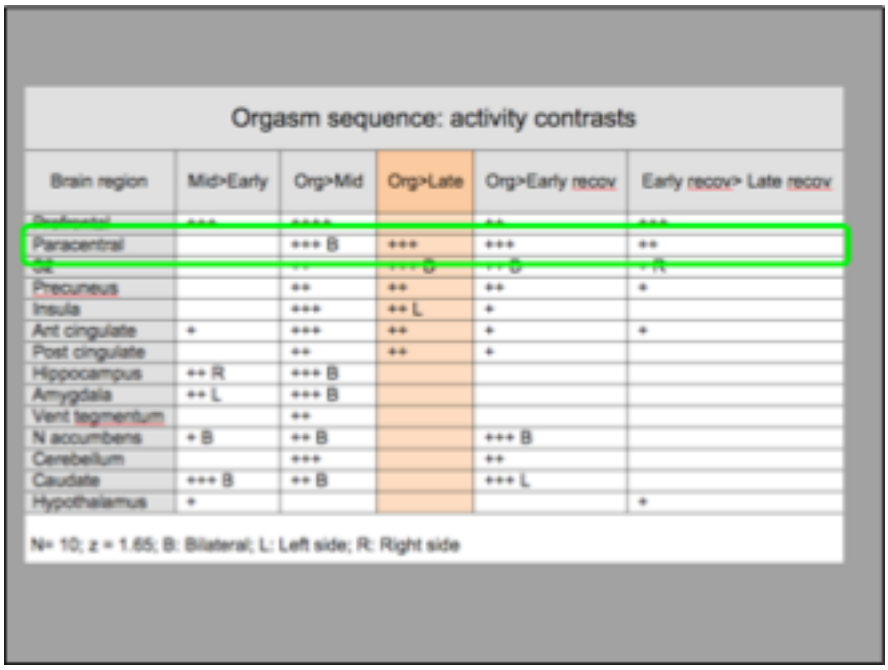


Orgasm sequence: activity contrasts

Brain region	Mid>Early	Org>Mid	Org>Late	Org>Early recov	Early recov> Late recov
Prefrontal	+++	++++		++	+++
S2		++	+++ B	++ B	+ R
Precuneus		++	++	++	+
Insula		+++	++ L	+	
Ant cingulate	+	+++	++	+	+
Post cingulate		++	++	+	
Hippocampus	++ R	+++ B			
Amygdala	++ L	+++ B			
Vent tegmentum		++			
N accumbens	+ B	++ B		+++ B	
Cerebellum		+++		++	
Caudate	+++ B	++ B		+++ L	
Hypothalamus	+				+

N= 10; z = 1.65; B: Bilateral; L: Left side; R: Right side

When we look at the activity of the prefrontal cortex, we see that it is active throughout the stimulation, orgasm, and recovery sequences. The blank space in the orange column indicates that activity of the prefrontal cortex does not significantly change in the transition period to orgasm. There was no evidence of deactivation at orgasm for the prefrontal cortex, amygdala, or any other brain region.

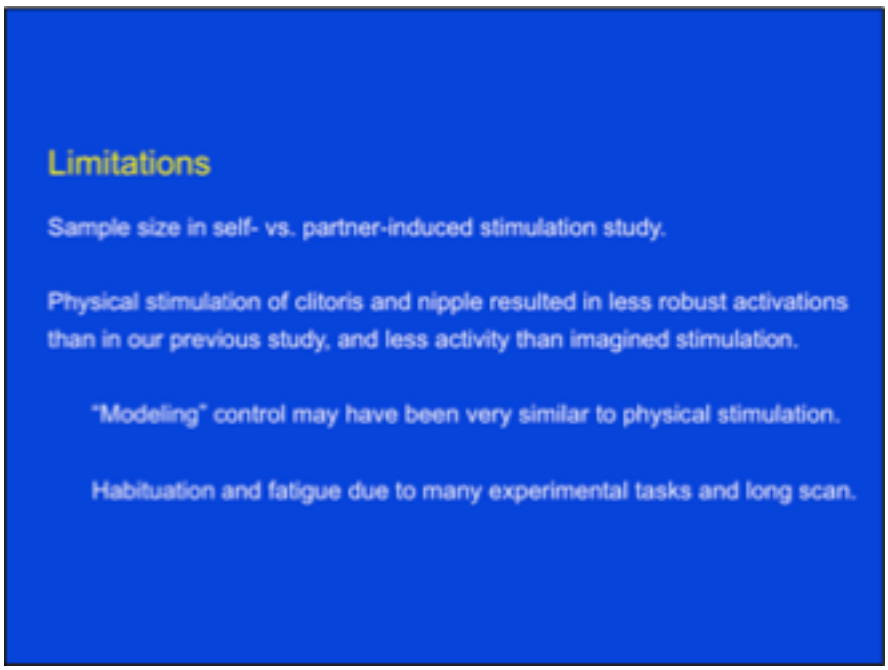


Orgasm sequence: activity contrasts

Brain region	Mid>Early	Org>Mid	Org>Late	Org>Early recov	Early recov> Late recov
Paracentral		+++ B	+++	+++	++
Precuneus		++	++	++	+
Insula		+++	++ L	+	
Ant cingulate	+	+++	++	+	+
Post cingulate		++	++	+	
Hippocampus	++ R	+++ B			
Amygdala	++ L	+++ B			
Vent tegmentum		++			
N accumbens	+ B	++ B		+++ B	
Cerebellum		+++		++	
Caudate	+++ B	++ B		+++ L	
Hypothalamus	+				+

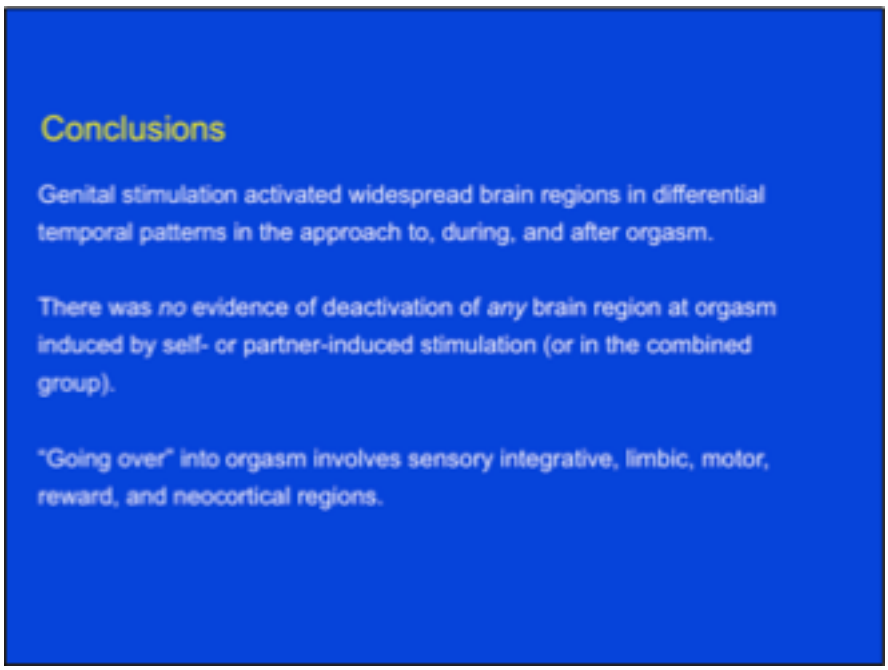
N= 10; z = 1.65; B: Bilateral; L: Left side; R: Right side

A view of the activity contrasts for the genital sensory cortex (paracentral lobule) shows that it's activity increases significantly over the course of stimulation, at orgasm, and that it remains active into recovery.



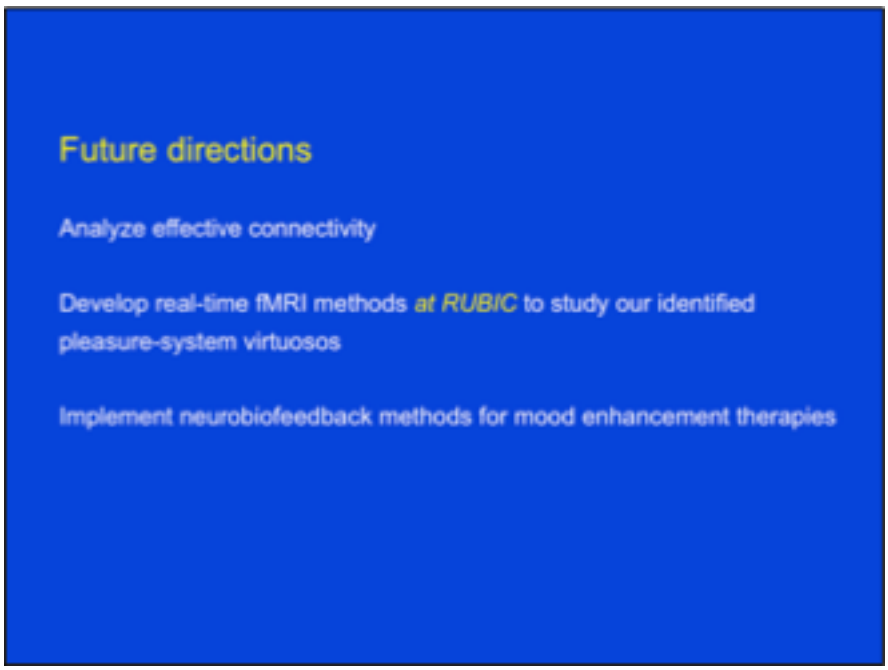
The major limitation of the orgasm study was the small sample size in the self-vs-partner-induced stimulation groups. More participants are needed to increase the N. With a larger sample size, we would likely be able to increase the statistical threshold for the going-over-into orgasm analysis, increasing the number of regions participating in the transition.

A limitation of study 1 is that physical stimulation of the clitoris and nipple resulted in less robust activations than in our previous study, and less activity than in the imagined stimulation conditions. A possible explanation is that the modeling control may have been very similar to physical stimulation, thereby reducing the difference between the control condition and the condition of interest. This could have contributed to the relatively low activity seen in the physical stimulation conditions. Habituation and fatigue due to the many experimental tasks and long duration of the scan might have also played a role in the less –robust- than expected findings for physical stimulation of the clitoris and nipple.

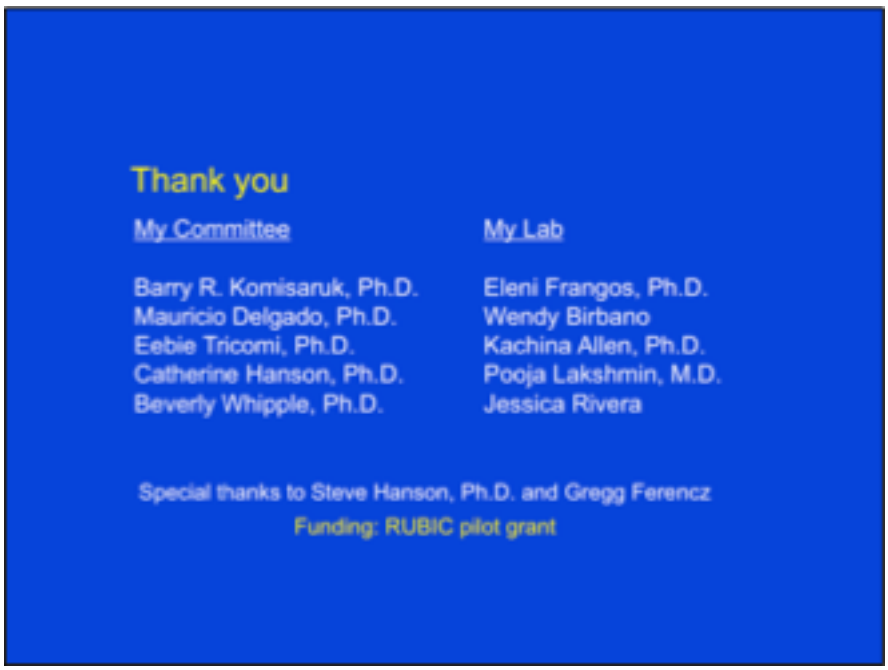


Conclusions: Genital stimulation recruits widespread brain regions in differential temporal patterns during the approach to, during, and after orgasm. There was no evidence of deactivation of **any** brain region at orgasm induced by self-or-partner- induced stimulation, or in the combined group. Going-over into orgasm involves sensory integrative, limbic, motor, reward and neocortical regions. Orgasm is a big brain event.

The knowledge gained by my dissertation research is a step toward clarifying the role that the sensory representation of the female genitals may play in sexual disorders. We need to understand how things work before we can intervene when things don't, for example in for example, in anorgasmia. More work is needed to facilitate the development of effective treatments for Persistent genital arousal disorder dyspareunia--painful intercourse, vulvodynia—vulvar pain, and other pelvic pain syndromes.



Future directions include to analyze the effective connectivity of the brain regions activated during stimulation, orgasm, and recovery to explore how these regions interact. A big step in this work would be to develop real time fMRI methods at RUBIC so that we can study our pleasure system virtuosos at play to gain insights —and apply this knowledge toward implementing neurobiofeedback methods for mood enhancement therapies.



A big thank you to my committee members, Barry, Mauricio, Eebie, Catherine, and Beverly. You have all been wonderful. To my advisor, dear Barry, words fail to communicate my appreciation. To my mentor, Beverly, you are the reason why I am standing here! And to my lab-mates, Eleni, Wendy, Kachina, Pooja, and our newest member, Jessica, I literally couldn't have done it without you ladies. A special thanks to RUBIC for giving me a pilot grant—and to Steve, Catherine and Gregg for making scanning there a pleasure.

And now, for questions?

CURRICULUM VITAE

GENERAL INFORMATION

Name: Nan Wise
Date/Place of Birth: September 10, 1957; Jersey City, New Jersey
Address: 11 Greentree Road, West Orange, New Jersey 07052
Phone: 973-632-0625
Email: nanellewise@gmail.com

EDUCATION

2009-2014	Ph.D. – Psychology – Concentration in Behavioral Neuroscience, Rutgers University - Newark
2008-2011	M.A. – Psychology, Rutgers University - Newark
1982-1985	M.S.W. – Rutgers University – New Brunswick
1974-1979	B.A.-Psychology, Rutgers- New Brunswick

PUBLICATIONS

1. Komisaruk, B. R., **Wise, N**., Frangos, E**.**, Liu, W.C., Allen, K., Brody, S. (2011) Women's clitoris, vagina and cervix mapped on the sensory cortex; fMRI evidence. Journal of Sexual Medicine. 8(10):2822-30.

POSTERS & ORAL PRESENTATIONS

1. Wise, N. (2014) Research plenary, Women's sexual health: *Where we have been and where we are going.* Whipple Family Research Plenary. The American Association of Sexuality Educators, Counselors, and Therapists. 46th Annual conference. Monterey, California.

9 Poster presentations can be found in Appendix G.

RESEARCH EXPERIENCE

2009-Present	Rutgers University – Newark Graduate student (Advisor: Barry R. Komisaruk, Ph.D.) Dissertation Project*: Genital stimulation, imagery, and orgasm in women: an fMRI analysis*

TEACHING

2009-Present	Teaching Assistant and part-time lecture Experimental psychology and statistics labs Rutgers University-Newark
2007-2009	Adjunct Professor Clinical Sexology Seton Hall University-South Orange