

Research report

Brain activation during vaginocervical self-stimulation and orgasm in women with complete spinal cord injury: fMRI evidence of mediation by the Vagus nerves

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Abstract

Women diagnosed with complete spinal cord injury (SCI) at T10 or above report vaginal–cervical perceptual awareness. To test whether the Vagus nerves, which bypass the spinal cord, provide the afferent pathway for this response, we hypothesized that the Nucleus Tractus Solitarius (NTS) region of the medulla oblongata, to which the Vagus nerves project, is activated by vaginal–cervical self-stimulation (CSS) in such women, as visualized by functional magnetic resonance imaging (fMRI). Regional blood oxygen level-dependent (BOLD) signal intensity was imaged during CSS and other motor and sensory procedures, using statistical parametric mapping (SPM) analysis with head motion artifact correction. Psychiatric examination and MRI established the location and extent of spinal cord injury. In order to demarcate the NTS, a gustatory stimulus and hand movement were used to activate the superior region of the NTS and the Nucleus Cuneatus adjacent to the inferior region of the NTS, respectively. Each of four women with interruption, or “complete” injury, of the spinal cord (ASIA criteria), and one woman with significant, but “incomplete” SCI, all at or above T10, showed activation of the inferior region of the NTS during CSS. Each woman showed analgesia, measured at the fingers, during CSS, confirming previous findings. Three women experienced orgasm during the CSS. The brain regions that showed activation during the orgasms included hypothalamic paraventricular nucleus, medial amygdala, anterior cingulate, frontal, parietal, and insular cortices, and cerebellum. We conclude that the Vagus nerves provide a spinal cord-bypass pathway for vaginal–cervical sensibility in women with complete spinal cord injury above the level of entry into spinal cord of the known genitospinal nerves.

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1. Introduction

Women diagnosed with complete spinal cord injury (SCI) above T10, i.e. above the level of entry into the spinal cord of the genitospinal sensory nerves, i.e. pudendal, pelvic and hypogastric [3,6,15,16,18,33,42,53], have been reported to

perceive, and respond with orgasms to, vaginal and/or cervical mechano-stimulation [30,69,67,80]. Since this level of SCI presumably blocks access to the brain of all the known genitospinal nerves, we proposed that the Vagus nerves convey the genital afferent activity directly to the brain, bypassing the spinal cord [37,30,35,80]. In order to test this hypothesis, we used functional magnetic resonance imaging (fMRI) to ascertain whether the region of the brainstem to which the Vagus nerves project, i.e. the Nucleus Tractus Solitarius in the medulla oblongata, is activated by vaginal–

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cervical self-stimulation in women with complete SCI or complete interruption of the spinal cord at or above T10.

There is direct evidence for a “genitosensory Vagus” based on the following studies in the laboratory rat. Guevara-Guzman et al. [51] reported that the nerve tracer, horseradish peroxidase, when injected into the cervix, produced labeling of neurons in the nodose ganglion, which is the dorsal root (i.e. sensory) ganglion of the Vagus nerve. Using Fluorogold, pseudorabies, DiI and CGRP immunoreactivity with neurectomy, the innervation of the uterus and cervix by the Vagus nerves was confirmed by Papka et al. [11]. Two separate studies provided functional evidence of a genital sensory role of the Vagus nerves. Thus, a response to vaginocervical stimulation that is mediated by the brain (i.e. pupil dilatation) persisted after spinal cord transection at T7; subsequent bilateral vagotomy abolished this response [36]. A different brain-mediated response to vaginocervical stimulation (i.e. increased vocalization threshold in response to forepaw electric shock) persisted after bilateral transection of pudendal, pelvic and hypogastric nerves; subsequent bilateral vagotomy also abolished this response [13]. In addition, neurons of the NTS were reported to respond to mechanical stimulation of the vagina, cervix, uterus, or rectum, and vagotomy altered these responses [26,27]. However, to our knowledge, there is no comparable direct evidence of a genital sensory function for the Vagus nerves in humans, although our preliminary findings using positron emission tomography suggested this possibility [40,38,79]. In the rat, the NTS shows a topographic organization, with gustatory responses occurring in the rostralmost region, gastric responses in the middle region, and intestinal responses in the caudal region [1,59]. We previously reported fMRI response to a gustatory stimulus in the superior NTS region in humans [39]. Consequently, in the present study, we expected that if responses to vaginal–cervical self-stimulation would occur in women with complete SCI at or above T10, the responses would be in the close vicinity of, but inferior to (i.e. closer to the spinal cord), their response to the gustatory stimulus.

Preliminary findings have been presented in abstract form [41,40].

2. Materials and methods

All procedures in the present study received prior approval from the Institutional Review Boards (IRBs) of Rutgers, The State University of New Jersey and the New Jersey Medical School of the University of Medicine and Dentistry of New Jersey, and each subject in the study signed an IRB-approved Informed Consent Form prior to her participation.

2.1. Participants

Each participant was interviewed by a clinical psychologist, within 2 weeks prior to fMRI testing, who screened

for psychosis or any condition that would contraindicate the woman’s participating in the study. None of the women was excluded. None of the participants had an oophorectomy or hysterectomy, prolapsed uterus, cysto-coele, recto-coele, or positive pregnancy test, based upon examination by their preferred gynecologist within 1 week prior to fMRI testing. Each had delivered one or two full term live births before her SCI. None had autonomic dysreflexia. None except ED (coded initials) described having imagery-induced orgasms. In four of the women, the SCI was produced by gunshot wounds. Their coded subject identifiers, age in years, and number of years since SCI, respectively, are: VA: 23, 5; EL: 40, 2; AN: 51, 3; AP: 54, 1. In one of the women, the SCI was produced by an automobile accident: ED: 51, 21.

2.2. Imaging

2.2.1. fMRI

Individuals were imaged in the coronal and sagittal planes using standard functional MR imaging BOLD techniques [58]. The individuals were imaged on a 1.5 T MR system from GE Medical Systems using gradient-echo echo-planar sequences (EPIBOLD) with the following acquisition parameters: 2000/40 (TR/TE); 64×64 matrix, 24 cm field of view, 4-mm-thick contiguous sections, and a 90° flip angle. For each motor or sensory paradigm, 140 images at each of 24 slice locations were obtained using a standard quadrature “bird cage” head coil. Coronal images were acquired in a plane parallel to the long axis of the brainstem and cervical spinal cord. Sagittal images were acquired using a coronal slice through the dorsal one-half of the pons and medulla as the localizer. Individuals’ heads were immobilized with foam and taped to the head holder to limit motion. Images were reconstructed from GE proprietary software (EPIRECON).

2.2.2. Anatomical images

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

2.2.3. MR images of the spine

In all subjects, sagittal and axial T1- and T2-weighted Fast Spin-Echo images of the cervical, thoracic and lumbar spine were acquired using standard phased-array coils. Images of the spine were interpreted by a neuroradiologist (AJK).

2.2.4. Data analysis

Statistical parametric mapping (SPM) was utilized. In SPM, the blood oxygenation level dependent (BOLD) [49] signal intensity of each voxel during the stimulus conditions was compared statistically with its activity during the pre-stimulus conditions. The resultant map was then displayed on a co-registered anatomical MR image [20]. In all cases,

pixels shown are at a significance criterion of $p=0.05$ or less (Bonferroni uncorrected). Motion correction was applied. Image data sets were processed without smoothing [82].

2.2.5. Task paradigms

The participants performed tasks designed to preferentially activate sensory nuclei superior and lateral to the NTS in order to demarcate the location of the NTS, as in our previous study [39]. These were, in sequence: (1) finger-tapping: self-paced bilateral finger to thumb apposition task of four cycles of 30 s ON, 30 s OFF to activate Nucleus Cuneatus, which is dorsolateral to the NTS; (2) gustatory: individuals self-administered a viscous mixture of sweet, sour, salty and bitter agents (sucrose, lemon juice, table salt, and dry mustard) into the oral cavity through a long flexible plastic catheter and maintained the mixture in the oral cavity for a period of 30 s, alternated with a 90-s period in which no substance remained in the mouth, for two cycles, in order to activate the superior region of the Nucleus Tractus Solitarius [39]; and (3) vaginal–cervical self-stimulation was applied for 28 s ON and 32 s OFF for 8 or 12 successive cycles and was repeated again after approx. 30 min.

2.2.6. The vaginal–cervical stimulator

Vaginal–cervical self-stimulation was applied with a passive stimulator [37] consisting of a handle into which a modified tampon mounted on a lucite rod was inserted at right angles. A Velcro® disc was attached to the tip of the tampon. To a ring pessary (Model PRSFS, Milex Products, Chicago, IL), previously fitted to each subject by her gynecologist, was

attached by suture silk a matching Velcro® disc. The pessary was inserted by a registered nurse and the Velcro® disc attached to the tampon stimulator was pressed against the matching Velcro® disc on the pessary. This device centered the stimulator tip against the cervix through the pessary and the pessary protected the cervix. See Komisaruk et al. [37] for a photograph of the stimulator.

2.2.7. Clinical diagnosis

At the study site, within 1 day of the fMRI testing, each of the women was examined by a physiatrist, who ascertained the level and completeness of the spinal cord injury using the standard ASIA examination method and criteria [2], in which sensibility is tested to a cotton wisp brushed against the skin and to a pinprick administered along the body surface. The ASIA standard test also evaluates whether there is awareness of digital anal stimulation. In addition, it was possible to acquire artifact-free MRI images of the site of spinal cord injury in three of the women, which were assessed by a neuroradiologist (AJK).

3. Results

3.1. fMRI evidence that cervical self-stimulation activates the projection zone of the Vagus nerves in women with complete spinal cord injury

Fig. 1 is a composite of 5 different women with spinal cord injury showing, in coronal view, that in each case there was activation of the region of the NTS of the medulla

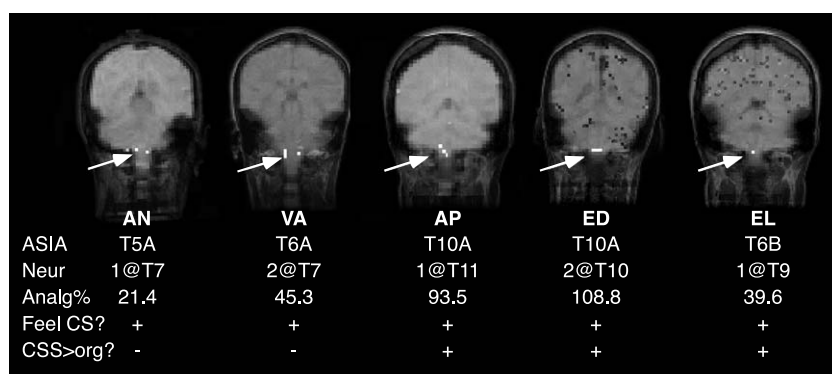


Fig. 1. Consistency of location of fMRI responses to cervical self-stimulation in five women with spinal cord injury, and their associated perceptual responses. Each of the five women with spinal cord injury showed activation of the region of the Nucleus Tractus Solitarius (NTS) (arrows) in response to cervical self-stimulation (women's initials: AN to EL). For each of the images, p values were set to the highest level at which activation of the region of the NTS was still visible. From L to R, the p -value thresholds are: 0.0001, 0.005, 0.001, 0.05, and 0.005, respectively. The ASIA criteria signify the lowest dermatomal level at which normal bilateral cutaneous (pinprick and/or cotton wisp) sensibility exists. "A" signifies "complete" spinal cord injury, i.e. no sensation or voluntary movement below that level, and no awareness of digital anal stimulation; "B" signifies "incomplete" injury; in this case, there was no sensation or voluntary movement below the level of injury, but there was awareness of digital anal stimulation. The label "Neur" is the more stringent categorization of the injury that we used in our previous study of women with spinal cord injury—i.e. the lowest level at which there was any sensation at all, rather than the ASIA criterion of the lowest level of "normal" sensation. The number "1" signifies partial (i.e. impaired) sensibility and the number "2" signifies normal sensibility. Thus, "1@T7" in the case of AN signifies that there was impaired sensibility at T7, but no sensibility below T7, and "2@T7" in the case of VA signifies that there was normal sensibility at T7, but no sensibility below T7. *Analg%* is the percent increase in pain detection threshold measured at the fingertips in response to cervical self-stimulation. *Feel CS?*: the "+" symbol signifies that each of the women reported feeling the cervical stimulator when it was inserted by one of the women investigators. *CSS>org?*: "+" signifies that orgasm was reported in response to the cervical self-stimulation, whereas "-" signifies that it was not. Relatively few pixels were activated in the region of the NTS in relation to the cervical self-stimulation; those that were activated were highlighted for clarity.

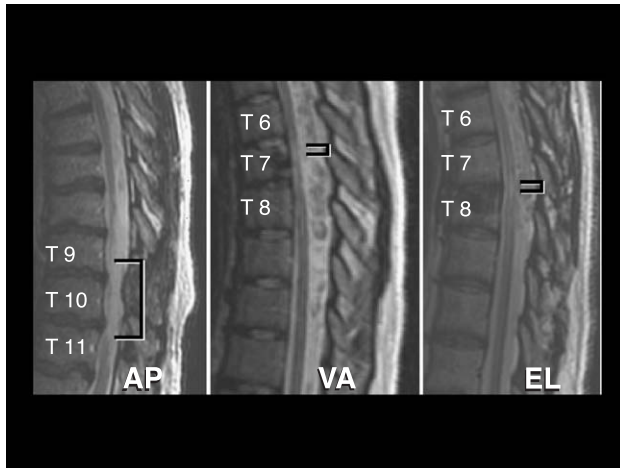


Fig. 2. The spinal cord injuries are at a level that would compromise the intraspinal afferent pathways from the vagina, cervix, uterus and clitoris. MRIs of three of the women, each of whose spinal cord injury was caused by a bullet wound. Based on their clinical diagnosis, the spinal cord injury of AP and VA was “complete” and that of EL was “incomplete.” The MRI’s show interruption or significant damage to the spinal cord *above* T10, which is the highest reported level of entry into the spinal cord of hypogastric nerve roots that can convey sensory activity from the uterus and cervix. The other genitospinal sensory nerves (pelvic and pudendal) enter the spinal cord at the sacral and lumbar levels.

oblongata during CSS. Note the similarity of location of the responses. Each of the activated sites is at a posterior “section” through the medulla oblongata in each of the women; the NTS is closer to the posterior portion of the

medulla than to its anterior portion. The region of activation is at the level of the base of the cerebellum.

The level and completeness of the spinal cord injury are specified below each image. Two of the women—AN and VA—had no sensibility below T7. They experienced an increase in pain detection threshold measured at the fingers in response to CSS—by 21.4% and 45.3%, respectively, over resting control levels. In addition, immediately before testing the pain thresholds, when the stimulator was inserted against the cervix, AN described a feeling of changing pressure as the stimulator was moved, and VA described a feeling of a “chill inside” that increased if increasing pressure was exerted against the cervix. The perceptual responses to CSS reported by these two women were consistent with our previous findings in other women with comparable completeness and dermatomal levels of spinal cord injury [37].

Subject AP had normal bilateral sensibility as low as T10, impaired sensibility at T11, and no sensibility below T11. The neuroradiologist reported the MRI of subject AP as showing a complete interruption of the spinal cord from mid T9 to upper T11, i.e. at a level higher than the clinical diagnosis indicated (Fig. 2, AP). Subject AP described a feeling of “touch inside” when the stimulator was inserted against the cervix. She showed a 93.5% increase in pain detection threshold during the CSS.

Subject ED had normal sensibility at T10 but none below that level. She stated that she can feel stimulation of the anterior vaginal wall, and she showed the greatest

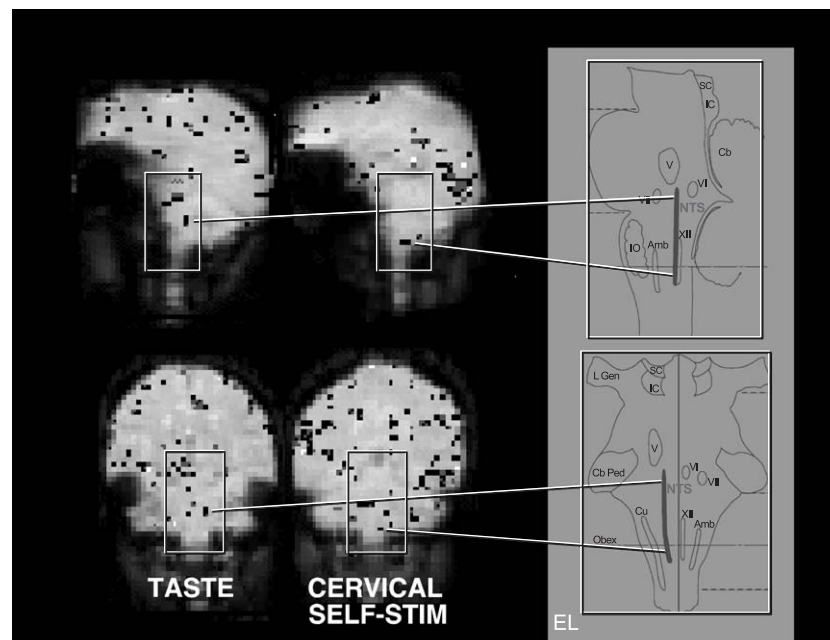


Fig. 3. Functional localization of the NTS. Sagittal (top pair) and coronal (bottom pair) fMRIs in response to a gustatory stimulus (a sweet–sour–salty–bitter sauce), which, based on laboratory animal studies, was expected to activate the superior region of the NTS, in comparison with the response to cervical self-stimulation. A schematic diagram of the location of the NTS in the medulla and pons (sagittal above and coronal below), adapted from Netter (1986), indicates that the response to cervical self-stimulation occurred at a location near the inferiormost region of the NTS by contrast with the response to the gustatory stimulus.

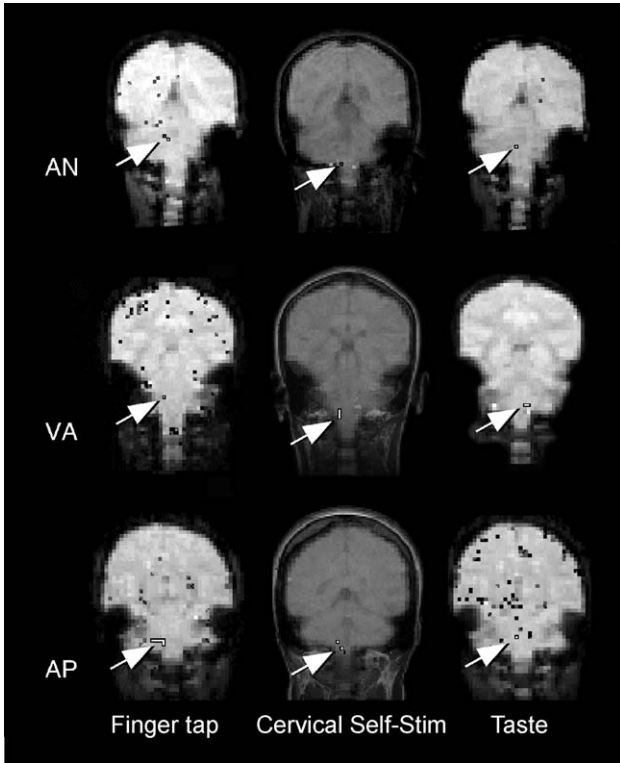


Fig. 4. Evidence of the resolving power of fMRI, showing differential activation of brainstem regions (coronal views) in response to three different stimuli—the gustatory stimulus, which was expected to activate the superior region of the NTS, cervical self-stimulation, which was hypothesized to activate the inferior region of the NTS, and finger tapping, which was expected to activate the Nucleus Cuneatus, which is lateral to the NTS. Note the consistency of the differential localization of responses among the three different women (AN, VA, AP). For clarity, the relevant activated pixels are indicated by the arrows and are highlighted.

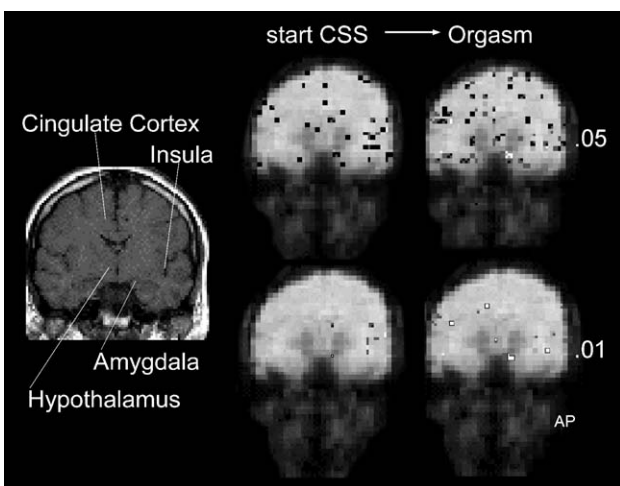


Fig. 5. Brain regions activated during orgasm induced by cervical self-stimulation (CSS)-induced orgasm in participant AP, whose spinal cord appears to be transected (Fig. 2). The image at the left of this figure shows the MRI anatomical image of the same brain. The lower pair of coronal views shows more delimited activation visualized at a more stringent criterion ($p=0.01$) than the upper pair of views ($p=0.05$). The indicated pixels have been highlighted for clarity.

magnitude of elevation of pain detection threshold—108.8%.

Each of the above four women fulfilled the ASIA criterion of “complete” spinal cord injury in that they failed to report sensory awareness of digital anal stimulation. Subject EL had no cutaneous sensibility below T9; however, she did have awareness of digital anal stimulation, and was consequently diagnosed as having an “incomplete” spinal cord injury. The spinal cord MRI of EL showed spinal cord injury in the form of a syrinx (i.e. a pathological tubular cavity) at T7–8, although it is not clear whether the spinal cord was completely interrupted (Fig. 2, EL). She stated that she had a sensation of “touch inside” and of vaginal muscle contraction when the stimulator was inserted. EL showed an increase in pain detection threshold of 39.6%.

3.2. Functional demarcation of the nucleus of the solitary tract

The region of the medulla oblongata activated by CSS was directly inferior to that activated by the control,

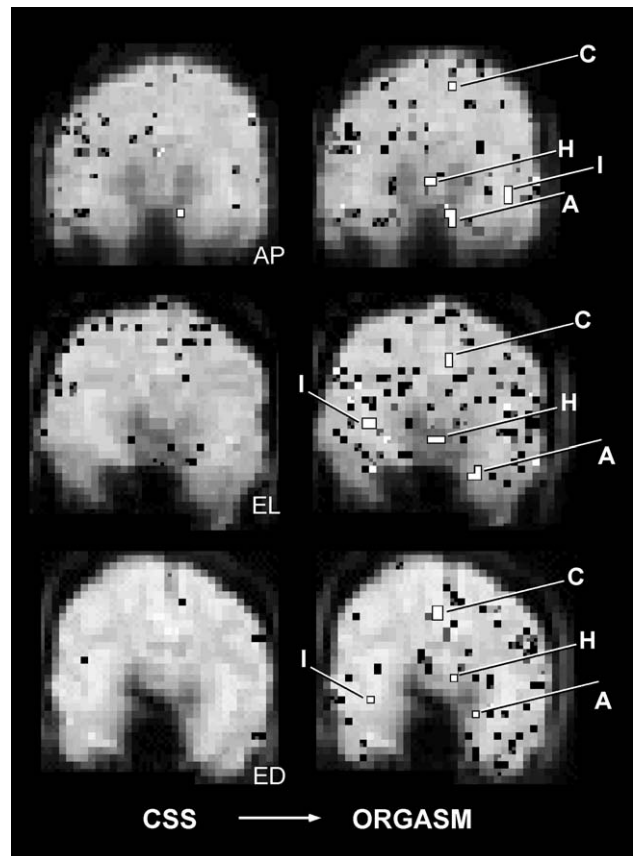


Fig. 6. Common regions of activation in the forebrain (coronal views) during orgasm in three of the women. The images in the left column show the activity during CSS, but when orgasm did not occur; the images in the right column show the activity during orgasm induced by the CSS. Abbreviations: A: Amygdala, H: Hypothalamus, C: Cingulate Cortex, I: Insula. The pixels indicated by the identification lines have been highlighted for clarity.

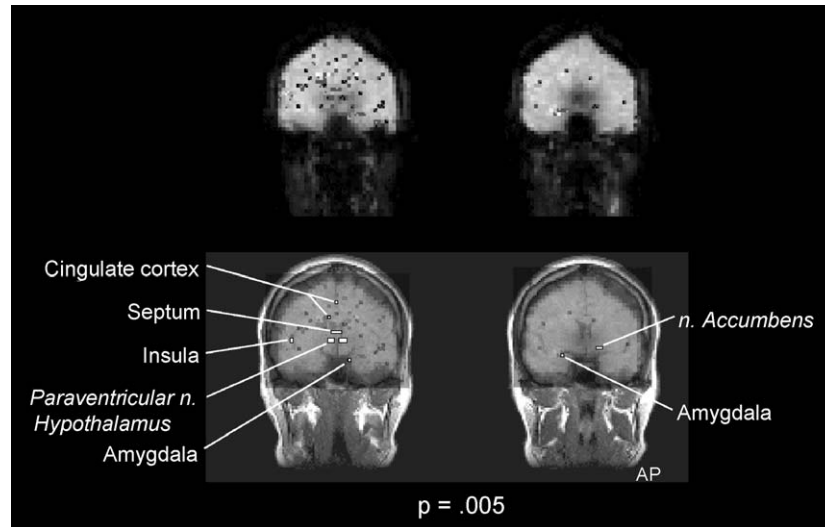


Fig. 7. Additional regions of activation in the forebrain during orgasm. A stringent criterion ($p=0.005$) was used for these data. The “raw” fMRI data are shown in the two adjacent coronal views above, and are shown superimposed on the anatomical brain images in the lower pair. The relevant pixels are highlighted for clarity.

gustatory stimulus, as seen in Fig. 3. The location of these regions of activation are shown in coronal and sagittal views, in relation to comparable schematic diagrams of the location of the NTS based on human brain atlases [50,52].

As another localization control, tapping the fingers was expected to activate the sensory relay—nucleus cuneatus—

which is lateral and adjacent to NTS in the medulla oblongata. As summarized in Fig. 4, the region of the medulla oblongata that was activated by CSS was distinct from that activated by finger tapping and the gustatory stimulus. Data are shown for the three women who had the clearest cases of disruption of the vaginal–cervical afferents through the spinal cord.

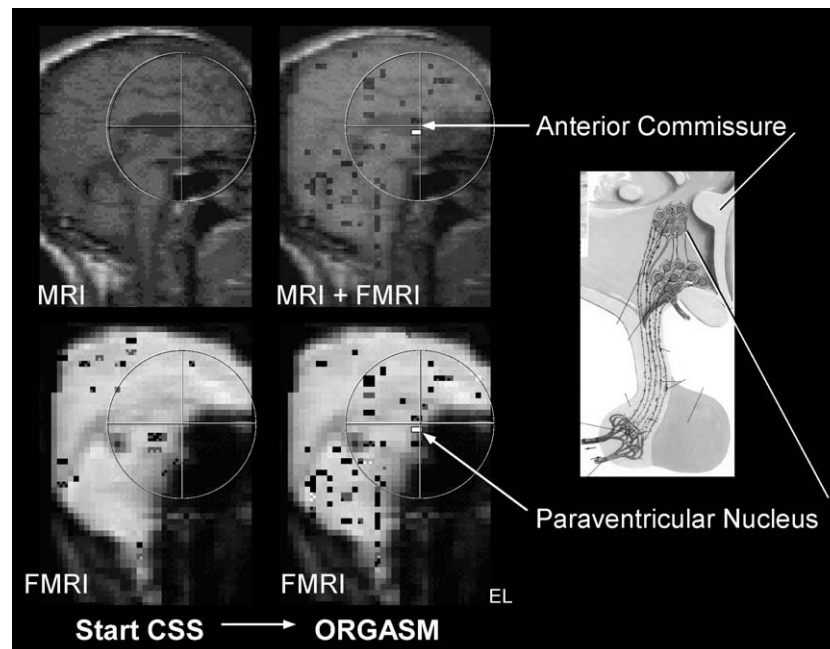


Fig. 8. Another example of activation of the region of the paraventricular nucleus of the hypothalamus at orgasm. This nucleus is localized in relation to the anterior commissure, as shown in the slightly modified schematic diagram of Netter [18]. The MRI (upper left) shows the midline sagittal anatomical view, the two lower images are “raw” fMRI images showing the activity during cervical self-stimulation (CSS) prior to orgasm (bottom left) and then at orgasm (bottom right). The fMRI activity at orgasm is superimposed on the anatomical MRI image (upper right). The crosshairs are situated at the anterior commissure. Note that the activated pixels (highlighted) are located slightly inferior and posterior to the anterior commissure.

3.3. Brain regions activated during orgasm in women with complete spinal cord injury: fMRI data

Fig. 5 shows that brain regions activated during orgasm included hypothalamus, medial amygdala, cingulate cortex, and insular cortex.

Among the three women who experienced orgasm during the CSS, similarity of brain regions activated at orgasm is shown in Fig. 6. Note the consistently higher overall activity during orgasm than during cervical self-stimulation prior to orgasm.

Fig. 7 shows fMRI images at orgasm in two different brain regions—the hypothalamus (upper and lower images on the left) and rostral to that, the preoptic/bed nucleus of the stria terminalis region (upper and lower images on the right). Note the activation in the region of the paraventricular nucleus of the hypothalamus, medial amygdala, cingulate cortex, insular cortex, and region of the nucleus accumbens.

Fig. 8 shows fMRI activity in the region of the paraventricular nucleus of the hypothalamus during orgasm. Note the activation in the region of the paraventricular nucleus occurring at, but not prior to, orgasm.

Fig. 9 shows a greater activation of hippocampus and frontal and parietal cortices at orgasm than at the onset of CSS.

The cerebellum showed an increase in activity during CSS-induced orgasm compared with the activity shown during CSS prior to orgasm (Fig. 10).

Fig. 11 shows a sequence of activation of forebrain components as orgasm developed in one of the women (EL) during continuous CSS over an 8-min period. Initially, none of the seven brain regions was activated, but over the course of the 8-min period leading up to orgasm, first the medial amygdala, basal ganglia, and insula showed the earliest activation, then the cingulate

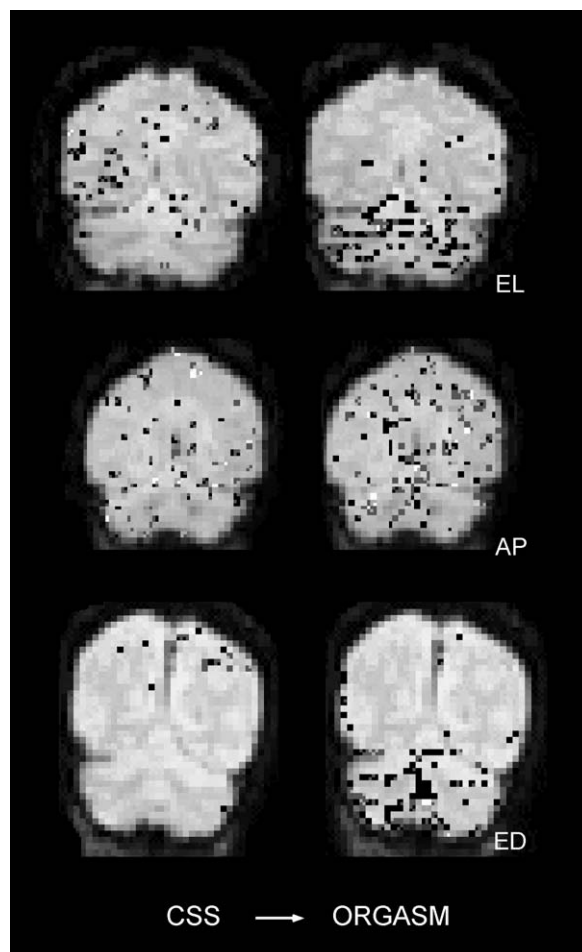


Fig. 10. Coronal view at the level of the cerebellum in the three women who experienced orgasm in response to CSS.

cortex added to this activation, and at orgasm, the nucleus accumbens, paraventricular nucleus of the hypothalamus, and hippocampus became activated. In addition, the

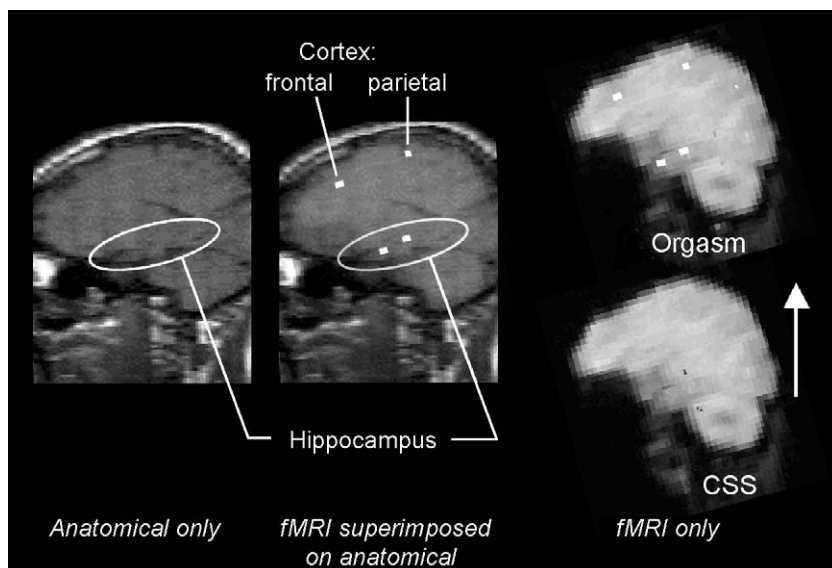


Fig. 9. Sagittal view showing activation in the region of the hippocampus and the frontal and parietal cortices (highlighted) at orgasm.

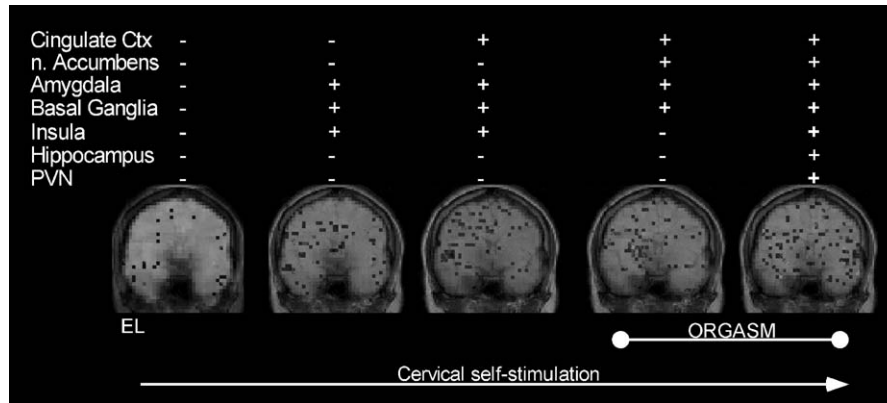


Fig. 11. Gradual increase in brain regions activated during cervical self-stimulation leading up to, and during, orgasm. Note that at the start of the stimulation, none of the seven brain regions showed activation (all “-”), whereas at orgasm each of these seven areas was activated (all “+”). The first two and last three of the eight 1-min data blocks, which were analyzed individually rather than cumulatively, are shown.

activation of insula and basal ganglia became more extensive.

4. Discussion

Subjects AN and VA constitute the clearest cases of brain responsiveness to CSS despite compromise of the known vaginal–cervical afferent pathways through the spinal cord to the brain. Since there was clear evidence of activation of the region of the NTS in response to CSS in these two women, they provide the best evidence for the existence of an extraspinal vaginal–cervical afferent pathway via the Vagus nerves. The level of spinal cord injury in subjects AP and ED would have eliminated input via the pelvic, and pudendal and all but the most superior branches of the hypogastric nerves, and they, too, showed distinct activation of the region of the NTS in response to CSS. It should be noted that these two women—AP and ED—showed the strongest analgesic responses to the CSS among the subjects (93.5% and 108.8%, respectively), indeed, well above the average of about 50% for non-injured women. Based on the magnitude of the analgesia response of ED, which was twice the average magnitude in non-injured women in our previous studies [37,34,77,78], it seems unlikely that the response could be due just to the hypogastric nerve component that enters the spinal cord at T10. The strong response in this subject, combined with the finding of her NTS response to CSS, supports a supplemental role for the Vagus nerves.

The discrepancy in AP between the clinical diagnosis (impaired sensibility as low as T11) and the radiological interpretation of her MRI (interruption of the spinal cord at T9) could be due to intact neural tissue that was not visible in the MRI, and/or to compensatory extension of dermatomal sensitivity from intact neural tissue above the level of the injury. In this regard, the critical question for the present study is whether afferents from the hypogastric nerve that normally enter the spinal cord at T10–12 [6,48] were

functional in this case. While the existing data cannot rule out the possibility that hypogastric afferents were functional, placed in the context of subjects AN and VA, who have complete spinal cord injury in which there was no cutaneous sensibility below T7, and who had similar perceptual responses and NTS activation, we believe that the data obtained from AP are consistent with a vaginal–cervical sensory role for the Vagus nerves.

While subject EL, who also showed CSS-related activation of the region of NTS, had no cutaneous sensibility below T9, she showed awareness of digital rectal stimulation. The conventional interpretation in this case would be that some afferent activity persisted through the spinal cord. However, in the context of the present study, an alternative interpretation should be considered, i.e. that a component of the Vagus nerve could convey this afferent activity. This interpretation is supported by a report [72] that three men and two women with surgical transection of the spinal cord at levels T4–10 perceived “dull pelvic sensation” in response to experimental rectal distention. Furthermore, the sensation persisted after sacral deafferentation.

It is also plausible that the CSS-produced analgesia observed in the present study could be mediated by the Vagus nerves. The present findings that CSS produced analgesia measured at the fingers in women with complete spinal cord injury above T10 confirms our previous findings of this effect [37,30,80], and is consistent with reports that electrical stimulation of the Vagus nerves can produce analgesia in humans [28] and also in the rat [43,47,60]. In the rat, vaginocervical pressure stimulation produced analgesia in the forepaws. This analgesia persisted even after bilateral transection of the known genitospinal nerves (pudendal, pelvic, and hypogastric), but was abolished after subsequent bilateral transection of the Vagus nerves [14].

Consistent with our findings [37,30,80], Sipski et al. [66,70] reported that women with complete spinal cord injury at various levels experience orgasm. They proposed that “orgasm is a reflex response of the autonomic nervous

system. . .” They hypothesized that “the sensory experience of orgasm. . . may occur without cerebral transmission of impulses, similar to menstrual sensations or the urge to void or defecate in SCI (spinal cord injury) patients with high-level complete injuries [68].” It is difficult to envision how any perceptions could occur in the absence of “cerebral transmission of impulses.” The concept of Sipski and colleagues does not refute the present evidence of a vagal genital afferent pathway in women.

There appeared to be an overall increase in brain activation at orgasm in the present study in which activation of specific and multiple brain regions could be discerned. These brain regions included hypothalamus, limbic system (including medial amygdala, hippocampus, cingulate cortex and insular cortex, and the region of the accumbens-bed nucleus of the stria terminalis-preoptic area), neocortex (including parietal and frontal cortices), basal ganglia (especially putamen), and cerebellum, in addition to lower brainstem (central gray, mesencephalic reticular formation, and Nucleus of the Solitary Tract [NTS]). A sequence of activation of different forebrain regions was observed leading up to CSS-induced orgasm. The earliest regions to show activation were the medial amygdala, insula, and basal ganglia, and at orgasm, added to these activated regions and the cingulate cortex, were the nucleus accumbens, paraventricular nucleus of the hypothalamus, and hippocampus. Differences between regional activation during, versus before or after, orgasm suggest that areas more directly related to orgasm include paraventricular area of the hypothalamus, medial amygdala, anterior cingulate region of the limbic cortex, and region of the nucleus accumbens. At present, we cannot distinguish whether these regions are activated uniquely at orgasm, or whether their activity increases gradually, only exceeding an arbitrary detection threshold at orgasm.

While there is no evidence of orgasm in female rats, some of the same brain regions have been reported to become activated during mating or vaginocervical stimulation. Thus, using the *c-fos* immunocytochemical method, activation was reported in amygdala [17,55,62,73,75,76], medial preoptic area [17,73,76], paraventricular nucleus of the hypothalamus [55,62], and based on local release of dopamine, the nucleus accumbens [56]. In rats, dopaminergic activity in the nucleus accumbens has been related to the “anticipatory phase of behavior” [63] and neuronal activity in the amygdala to “reward expectation” [64].

To our knowledge, this is the first evidence of activation of hypothalamus during orgasm in men or women. Earlier reports of orgasm in men found activation in prefrontal cortex, but not subcortical structures [74]. Recently, Holstege et al. using positron emission tomography reported that during orgasm, elicited in men by penile stimulation by a partner [21,24] and elicited in women by clitoral stimulation by a partner [25], the mesodiencephalic region, cerebellum, and several cortical areas, but not the hypothalamus, became activated. Furthermore, in men during

sexual arousal, but not orgasm, elicited by visual stimuli, Hagemann et al. [22] using positron emission tomography in men with erectile dysfunction, reported that the frontal cortex and anterior cingulate regions were activated, and Wallen et al. [23] using fMRI, reported that activity was increased in amygdala, hippocampus, and hypothalamus in men relative to the activity in women, whereas the striatal regions (caudate and nucleus accumbens) were activated in both men and women.

The finding of activation of PVN, observed in the present study, is consistent with reports of oxytocin release during orgasm. That is, the PVN neurons secrete oxytocin, which is stored in the posterior pituitary [12], vaginal or cervical stimulation releases the oxytocin from the posterior pituitary gland into the bloodstream—a response known as the Ferguson Reflex [19]—and orgasm releases oxytocin into the bloodstream [5,8,9]. Furthermore, the activation of cingulate cortex and medial amygdala observed during orgasm in the present study could also play a role in oxytocin release on the basis of reports that uterine contractions are elicited by electrical stimulation of cingulate cortex [4] in cats and medial amygdala [65] in rabbits.

In the rat, electrical stimulation of the Vagus nerve releases oxytocin into the bloodstream [46] and the NTS has major reciprocal connections with the PVN and the amygdala [61]. Furthermore, vagal electrical stimulation produces analgesia in the rat [60] and human [29] and oxytocin produces analgesia in the rat [54] and human [81]. Thus, there is precedence for the perceptual, neural, and neuroendocrine events of orgasm to be elicitable by vaginocervical stimulation that could access the brain via the Vagus nerve, rather than the spinal cord.

It is of interest that during orgasm, the insular cortex and anterior cingulate cortices are active, because both of these areas have been reported to be activated during response to pain [7,10,57]. This suggests the existence of a local interaction between the pain and orgasmic pleasure-related regions of the brain, and a possible site involved in the analgesia produced by CSS.

The nucleus accumbens also showed activation during orgasm in the present study. This brain region has been reported to show fMRI activation during the “rush” induced by an i.v. injection of nicotine [71]. Our findings suggest a role for the nucleus accumbens in mediating orgasmic pleasure in women. This is consistent with recent reports of activation during orgasm of the midbrain region in men, from which dopaminergic neurons originate [21,24].

A salient and reliable feature of brain regions activated during orgasm was activation of the cerebellum. The cerebellum modulates muscle tension via the gamma efferent system and it receives proprioceptive information [45]. Since muscle tension can reach peak levels during orgasm [44] and contribute to the sensory pleasure of orgasm [31,32], it is not unlikely that the cerebellum thereby plays a significant motoric and hedonic role in orgasm.

5. Conclusions

The above findings lead us to three major conclusions: (1) In women, the Vagus nerves provide a genital (vaginal–cervical) sensory pathway that bypasses the spinal cord, projecting directly to the brain, and thus can provide genital sensation despite interruption of the spinal cord at any level. Consequently, health care practitioners would be advised to not assume that women who suffer such injury can no longer experience genital sensation, and to specifically test for such sensibility in individual cases; (2) in cases of compromise of vaginal–cervical sensory activity via the genitospinal nerves, genital sensory activity conveyed via the Vagus nerves is evidently adequate to induce orgasm in some women. This provides a minimal and delimited (relative to ascending spinal cord activity) neural input that could facilitate elucidation of the neural mechanisms underlying orgasm; and (3) specific regions of the forebrain and upper and lower brainstem appear to be uniquely activated at orgasm.

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