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Review

A scientist's dilemma: Follow my hypothesis or my findings?

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ABSTRACT

Over the course of my 50 years of brain-behavioral research, choicepoints presented themselves as to either follow my original hypothesis or follow my puzzling empirical findings. I trusted the latter more than the former because I believe it is where reality is to be found. Phil Teitelbaum's teachings had a major influence on those decisions. In the present essay, I describe the evolution of those choicepoints that led me from studies of hormone-brain-behavior interactions to a rhythmical brain-behavior connection, to sexual behavior, pain blockage, human brain-behavior interactions, and human brain imaging. Along this tortuous course, I learned that vaginal stimulation can block pain, the vagus nerve apparently can convey genital sensory activity to the brain, bypassing spinal cord injury, and all major brain systems evidently contribute to women's orgasm. An important message I learned is: pay attention to what you observe in your experiments, and have the courage to follow it up, particularly if what you observe is not what you were looking for. . .because it, rather than your hypothesis, is more likely to reveal reality.

Phil Teitelbaum has been my scientific big brother, starting from when he was on my doctoral dissertation committee. I appreciated his insights, especially his metaphor about the brain being like a house – that you could look into its different windows, but it is the same house. What I took him to mean by that is that you can study different brain processes – feeding, drinking, sex behavior, hormone control, learning, memory – and there must be a unity among them, just as there is a unity among the different rooms of the house with their different mechanisms and functions. So Phil taught me to not be compartmentalized into studying a particular function. Phil's insights are always provocative, especially one that I still have difficulty grappling with. He pointed out that abolishing a behavior pattern by making a localized brain lesion doesn't mean that the region is normally critical for the control of that behavior pattern. Rather, it means that this is how the brain still functions in the absence of that region.

I once heard Phil say that he kicked himself all around the room when he was scooped by Brobeck on the critical role of the lateral hypothalamus in feeding behavior. When he had made those same lesions previously, his damn rats kept dying, so he figured he must be doing something wrong. He said it did not dawn on him that they were dying because they were starving to death! The message I got from Phil from that anecdote is that it depends on how you look at things. I had a similar self-kicking experience with my experiments on sniffing behavior in rats. James Olds asked me to see if there was any correlation between the activity of neurons in various brain regions (hypothalamus, hippocampus, reticular formation, etc.) in freely moving rats and the rats' behavior [1]. While trying to eliminate the EMG artifact produced by vibrissa movement during exploratory behavior, I realized that the movement was highly rhythmical at the same approximately 7/sec rate as the theta rhythm, and that the rats licked the water tube and chewed their food pellets at the same 7/sec rate. That made me think that there is 7/sec pacemaker for the theta rhythm that may be driving sniffing, licking, and chewing [2]. I was trying to locate the pacemaker for the rhythmical 7 per second sniffing movements in my rats, which I found to be synchronized with the 7 per second theta waves. I removed by suction ablation the entire cortex, basal ganglia, cerebellum, olfactory bulbs, and hippocampus, but they kept sniffing rhythmically. I got somewhere when I removed the septum, because that stopped the rhythmical sniffing – but it returned a few days later. Foiled again! Eventually, I just gave up trying. My self-kicking started years later when it dawned on me that I never considered a figure-ground reversal: recovery of function! What a great preparation in which to study the mechanism of recovery of a major brain-behavior connection!

Incidentally, in the course of removing the septum [3], I confirmed a weird but totally reliable effect that Phil had reported with Cytawa [4], namely that if you actually get your courage up enough to hold a septal rat (which you catch using a heavy glove and after it lands after hitting the ceiling when you first try to grab it), and turn it upside down, it suddenly goes limp in your hand, and may stay like that for tens of seconds, even if you release your grip on it. The contrast between the extraordinary hyper-responsiveness, when

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it can literally jump high enough to hit the ceiling, and moments later when it goes totally limp while inverted in one's hand, is for me almost as striking a neurobiological fact as orgasm.

The advent of functional Magnetic Resonance Imaging in the 1990s created an old trap that I see psychologists falling into – hi tech phrenology. In seminars, time after time, young investigators, skilled in fMRI analytical methodology, report brain localizations correlated with anticipation, frustration, anxiety, language, recognition, fear, etc. When I ask them what their identified brain region does to generate the perception or its related behavioral or physiological components, their typical answer is – that's a good question!

A similar trap was created when the technology for recording the activity of single neurons in awake animals was developed in the 1960s and applied to investigations of where learning occurs in the brain. When the activity of a single neuron was found to be correlated with the learning of a task, the obvious question was: to what aspect of the learning is the neuron's activity related? Is the neuron's activity related to a particular component of a new motor pattern, to attention to a particular component of a stimulus, or in some way to the learning process itself? And how is one to discern the differences?

In these fMRI studies and the single-neuron studies before them, indeed in any studies of brain function, when one finds a correlation between a brain region and behavior, it is instructive to ask, how what we know about that brain region could account for the behavior – a process termed "reverse engineering." I have been facing that problem essentially throughout my career with variable success, in my attempts to relate brain function to behavior. The following are some examples.

In my doctoral research with Danny Lehrman at Rutgers, I wanted to see if there is a specific brain site at which progesterone acts to stimulate incubation behavior and inhibit male courtship behavior in ring doves. I found that crystals of progesterone implanted in multiple brain sites – not just one brain site – would exert those behavioral effects [5]. Then I wanted to know what action the hormone exerts on the brain to affect the behavior. So I requested, and was granted, the opportunity to learn methodologies of brain recording with Charles H. Sawyer at UCLA, whose research group was the only one in the USA studying neuronal responses to hormone administration.

This research taught me an important lesson about apparent specificity of hormone action. A then recent publication by Barraclough and Cross [6] in urethane-anesthetized rats had claimed a rapid inhibitory effect of progesterone administered i.v. on only specific hypothalamic neurons. We repeated their study with the additional procedure of monitoring cortical EEG. We observed that under urethane, the brain spontaneously showed minutes-long periods when the EEG appeared sleeplike (high amplitude slow waves) alternating with minutes-long periods when the EEG appeared arousal-like (low amplitude fast waves). The firing rate of almost all the neurons in the cortex and thalamus, and about one-third of those in the hypothalamus spontaneously diminished during the sleeplike EEG and increased during the arousal-like EEG. Injection of progesterone i.v. induced an immediate long-duration continuous sleeplike EEG pattern, and all the neurons retained their previously-established, EEG- correlated pattern of activity. If we pinched a foot, thereby producing an arousal-like EEG pattern, the neurons continued to follow their individual characteristic correlation with the EEG. Thus, we replicated the findings of Barraclough and Cross, but by extending their findings by recording EEG concomitantly, we came to a very different conclusion. That is, what appeared to be a "specific" action of progesterone on only certain hypothalamic neurons turned out to be a general effect of progesterone on the arousal level of the brain to which some hypothalamic neurons were linked while others were independent. Only those hypothalamic neurons whose firing rate correlated with the EEG were affected by the progesterone, whereas those hypothalamic neurons whose firing rate was independent of the EEG fluctuations were unaffected by the progesterone. Thus, we refuted the evidence purporting a specific inhibitory effect of progesterone on hypothalamic neurons [7]. The lesson I learned from that study was to not assume that a change in brain activity is necessarily related to the behavioral or physiological endpoint in which we are interested.

Another example, developed from that same study with Sawyer, led to my finding that vaginal stimulation blocks responses to noxious stimulation, and raised the question of whether the effect was due to an actual blockage of pain. In that study, the reason for injecting progesterone was to ascertain whether it modulated the neuroendocrine reflex-induced pseudopregnancy response to vaginocervical stimulation. In a subsequent study of the activity of single neurons in awake, freely-moving rats in collaboration with James Olds, I again applied vaginocervical stimulation to see how it might affect neuronal activity. The stimulation had three immediate and surprising effects. First, it strongly inhibited the firing activity of neurons in the lateral hypothalamus (medial forebrain bundle). These neurons spontaneously increased their firing rate whenever the rats locomoted, and became inactive whenever the rats stood still [1]. To this day, I am not aware of another study implicating this very clear evidence of lateral hypothalamic involvement in locomotion. The second effect of the vaginocervical stimulation was a sudden lordosis response, in which every rat tested raised the rump and the head in the characteristic mating stance, regardless of the stage of their reproductive cycle [8]. We subsequently followed up these observations, finding that rats would show this lordosis response even after removal of the ovaries and pituitary – hence independent of ovarian hormones [9] – and that 1-second of vaginocervical stimulation would induce sexually unreceptive rats to mate [10]. The third surprising effect was that the vaginocervical stimulation immobilized the rats as soon as the probe touched the cervix. The immobilization was so strong that the rats could be slid, stiff-legged, along a table surface without locomoting away from the probe when no restraint or stimulation was applied, other than just the gentle force against the cervix. How strong is the immobilization; what happens if the paw is pinched? Normally, if a paw is pinched, the rat immediately withdraws the leg and vocalizes. During vaginocervical stimulation, if a paw is pinched, there is no leg withdrawal and no vocalization [11]. Is this a motor inhibition, a sensory inhibition, or both?

I came to a choice point in my career. I realized that I had to choose between continuing with the connection between rhythmical behavior and the theta rhythm on the one hand, versus following up on what might be a pain-blocking effect of vaginal stimulation. One day when I visited my wife in the hospital, trying in vain to console her suffering in pain from cancer, I said to myself don't just stand there like a dummy. If you think you're so smart, go do something useful and figure out how to block pain. I decided then and there that rhythmical brain activity as a driver for rhythmical behavior would be a nice theoretical pursuit, but a bigger challenge would be to do something useful for people in pain. So I shifted away from rhythmicity and focused on pain blockage.

To address my question of whether vaginocervical stimulation blocks pain, I recorded the responses of single neurons in the sensory thalamus to noxious (paw pinch) and innocuous (fur brushing) stimulation and found that vaginocervical stimulation inhibited the responses to the noxious, but not the innocuous stimuli, suggesting that analgesia was induced [12]. At that point I realized that the only way to know for sure whether vaginal or cervical stimulation blocks pain is to obtain a verbal report –i.e., ask women – which would be the most "scientific" answer to the question! We organized that study and found that vaginal and cervical self-stimulation significantly and markedly elevated pain thresholds, measured as the

force at which gradually increasing compression applied to the fingers begins to feel painful. When the self-stimulation was applied as continuous mild pressure, or in a way that feels pleasurable, or that induces orgasm, the increases in pain threshold were over 50%, 75%, and 100%, respectively. Moreover, tactile thresholds measured concurrently using von Frey fibers applied to the back of the hand, did not change significantly under any of those conditions. Consequently, we concluded that vaginal self-stimulation produces analgesia, i.e., a selective inhibition of pain but not touch [13,14].

The possible adaptive function of this analgesia is an intriguing question, about whose answer we can only speculate. In rats, because pregnancy fails if enforced sub-typical numbers of intromissions occur prior to ejaculation [15], but excessive multiple intromissions become aversive to the females [16], perhaps the analgesia that occurs during natural mating [17] renders the female rat willing to accept the multiple intromissions that are necessary for pregnancy. Analgesia also occurs in rats [18] and women [19] as the fetus is passing through the birth canal. Perhaps this reduces pain and stress of parturition and thereby promotes bonding between the new mother and the neonate.

Once we started on the road of research on humans, some of our questions were better answered in humans, whereas others in rats. Which nerves convey the vaginocervical signal and which neurotransmitter(s) in those neurons produce the inhibition? Those questions required studies in rats in which we recorded action potentials from the various genital sensory nerves [20,21] and transected them, and found that the major inhibitory role is played by the pelvic nerves, which convey afferent activity from the vagina and cervix [22]. Then we superfused the spinal cord, collected the effluent, and analyzed for vasoactive intestinal peptide (VIP), for this peptide occurs in differentially high concentration in the pelvic nerves [23]. We found VIP to be released into the spinal cord by vaginocervical stimulation [24]. Then we administered VIP, found that it had antinociceptive effects comparable to vaginocervical stimulation, administered fragments of VIP, one of which was more effective than the parent compound, and obtained a use patent for the fragment as an analgesia-producing agent [25]. In related studies, using superfusion of the spinal cord and selective neurotransmitter blocking agents, we found evidence of significant contributions to vaginal stimulation-produced antinoception also by GABA, glycine, norepinephrine, 5-HT, and endogenous opiates [26].

Then, to ascertain whether the pelvic nerve, rather than the other genital sensory nerves, has a comparable analgesia-producing capacity in women, we studied women with complete spinal cord injury at different levels of the spinal cord that would block access to the brain of the various genital sensory nerves. As the most stringent test, we included a group of women who had complete spinal cord injury at a cord level high enough (T10 and above) to block access to the brain of all the known genital sensory nerves. To our surprise, those women stated that they could feel the vaginal and cervical stimulation despite the fact that they had no trunk or leg sensation, or voluntary movement, below the level of their injury. They did tell us, however, that the one sensation that they still retained was menstrual discomfort. Furthermore, these women reported significant increases in pain threshold measured at the fingers, when they applied vaginal or cervical self-stimulation [27,28]. The most plausible explanation seemed to me to be that the vagus (10th cranial) nerves convey vaginal and cervical sensation, bypassing the spinal cord, although the classical view is that the vagus nerves project only as far as the abdominal organs, stopping short of the pelvic organs. However, the laboratory of Guevara–Guzman had published evidence a few years earlier that the tracer, horseradish peroxidase, injected into the cervix of rats, labeled the nodose ganglion, which is the dorsal root (sensory) ganglion of the vagus nerve [29]. I figured that the only way to test the genital sensory vagus hypothesis in women was to ascertain whether the Solitary Nucleus, which is the projection zone in the medulla oblongata of the sensory vagus, is activated by vaginal or cervical stimulation in the women with the high level of complete spinal cord injury.

To justify that study, I deemed it important to first obtain functional evidence of a genital sensory role for the vagus nerves in rats. I surgically removed a segment of spinal cord at the mid-thoracic level, applied vaginocervical stimulation, and observed that a response to this stimulus that we had published earlier, i.e., pupil dilatation, persisted in these spinal cord-ablated rats. Then I transected the vagus nerves in the same rats, and observed that the pupil dilatation response was abolished [30]. As a further confirmation, we applied electrodes to the cut central end of one vagus nerve and observed that electrical stimulation through the electrodes produced immediate and marked dilatation of both pupils [31].

Convinced that the vagus nerves can convey genital sensory activity directly to the brain, bypassing the spinal cord, I established a collaboration with the fMRI facility at the Department of Radiology at the University of Medicine and Dentistry of New Jersey in Newark. We first had to identify the Solitary Nucleus in humans using the fMRI, for which there were no publications. I figured that with reference to histological atlases of the human lower brainstem, we could triangulate on the Solitary Nucleus by activating the cranial nerve nuclei that surround it, particularly the facial and hypoglossal motor nuclei, and the trigeminal sensory nucleus. However, there were not any publications of cranial nerve nuclei activation using fMRI either. We had the participants in the fMRI scanner smile and pucker to activate the facial nucleus, tap the tongue against the roof of the mouth to activate the hypoglossal nucleus, and we tapped their face to activate the trigeminal nucleus. Then, based on reports in the rat literature that gustatory stimuli activate the Solitary Nucleus, I made a barbecue sauce of sugar, salt, lemon juice, and dry mustard to represent sweet, salty, sour, and bitter, and had our scanner participants take a sip through a tube (a heroic early morning effort on their part)! We published evidence of activation of each of these nuclei by our procedures [32]. It was particularly instructive to observe instances in which there was no fMRI activation whatsoever in a cranial nerve nucleus, e.g., the facial nucleus, despite the obvious intense and long-lasting (2.5 min total time) strong facial grimaces. That just goes to show that under the most obvious activation conditions, sometimes a large brain nucleus can appear to be completely inactive on the basis of fMRI activity measures!

Armed with the evidence of the location of the Solitary Nucleus, we then tested women with complete spinal cord injury at the high spinal cord level. We found that in each of the five women we tested, there was clear evidence of activation of the Solitary Nucleus location in the caudal medulla oblongata. Some of those women experienced orgasm during the vaginal and cervical self-stimulation. That enabled us to observe and be the first to report on brain regions activated during orgasm in women [33]. We are continuing those studies at present in able-bodied women [34] and men.

During orgasm in women, we see activation of genital sensory cortex and sensory thalamus, cerebellum, amygdala, hippocampus, prefrontal cortex, nucleus accumbens, and anterior hypothalamus. Based on notions of the role of these different brain regions in other contexts, we can speculate as to how they may generate components of orgasm, but we don't know if there is more to orgasm than the sum of those parts. For example, sensory thalamus and cortex are the initial entry route for genital activity and that stimulation continues throughout orgasm. While that finding in itself is not surprising, it does raise the "hard" question of how any sensation is created from the activation of neurons. What is unique

about the sensory cortex that enables its neurons to generate conscious awareness, whereas other of "our" neurons, such as in the spinal cord, can become active when detached from the brain (e.g., activation of spinal reflexes in persons with severed spinal cord) but not generate conscious awareness? Activation of the genital sensory cortex also raises the intriguing question of what is the difference between perception of genital sensation when it feels simply prosaic, as when sitting down, versus when it feels erotic.

What are the contributions of the other brain regions that become active at orgasm? We can make "just so" stories about the cerebellum perhaps contributing to the muscle tension of orgasm, the hippocampus providing fantasy, the amygdala stimulating the autonomic responses of tachycardia, hypertension, pupil dilatation, the prefrontal cortex controlling the "executive" orchestration of genital self-stimulation, the anterior hypothalamus providing the oxytocin secretion that peaks at orgasm, and the nucleus accumbens providing the pleasure – the latter being another, very "hard" question.

Even if all those reverse engineering notions are correct, we still do not know whether the "whole" of orgasm is greater than the sum of these parts. But at least I question how what is known about the roles of the various brain regions could contribute to the constellation of activity that comprises orgasm.

Of course it is possible to generate potentially useful new knowledge with this type of information despite not knowing the contributions of the various brain components. For example, we are using fMRI to study genital self-stimulation in persons who have lost the ability to elicit orgasms in an attempt to ascertain which of the brain regions fail to become activated. We hope to then develop a neurofeedback procedure to bypass the blockage. We are developing methodology to show the person in the scanner their own fMRI activity in near-real-time to ascertain whether they can learn to voluntarily activate brain regions beyond the blockage. We don't know the limits of the extent to which we can modify our own brain activity by seeing an actual representation of it, and which brain regions are susceptible to such voluntary control.

In conclusion, I have summarized some of my lessons learned in my 50 years of behavioral neuroscience research. It has been a tortuous path, but one that I took by following empirical observations that cropped up and seemed both reliable and puzzling. As three examples, the rats were not supposed to show lordosis during the "wrong" phase of their estrous cycle or after ovariectomy, but they did. The women with complete spinal cord injury weren't supposed to feel or respond to vaginal or cervical stimulation, but they did. The vagus nerves aren't supposed to project as far as the pelvic region, but apparently they do. I tell my students to pay attention to what doesn't make sense but keeps cropping up in their experiments, because those things are probably more real and likely to be more important than the hypotheses that they started out with. I have noticed that doctoral students often do not recognize or appreciate when they have made a real and important discovery, especially if it is not what they were looking for. My parting advice is: trust your observations, especially if they do not seem to make sense, and take a chance on following them up to try to figure out why they are happening. . .it could lead you to an important discovery. And try to remember my lesson learned from Phil. . .that to avoid kicking yourself around the room later, look into more than one window in the house now.

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