CHAPTER X: HOW CAN WE USE FUNCTIONAL IMAGING TO LOOK AT THE THERAPEUTIC EFFECT OF ACUPUNCTURE?

Well, what do these tools, what does this data begin to tell us and how can we use these tools of functional imaging to be able to actually look at the therapeutic effect of acupuncture?

For this, I'd like to turn to a very nice study performed by Joe Audette and again, our young faculty member, Vitali Napadow, who were studying carpal tunnel syndrome and the effects of acupuncture on carpal tunnel, but in this case not just the clinical effects, but the underlying brain effects, a very interesting study.

The first thing to know for those of you less familiar with carpal tunnel, as I was quite unfamiliar, is that carpal tunnel doesn't really just affect the wrist. It's well known, for example, that there are significant abnormalities, injuries to the median nerve, that they reflect themselves in delayed propagation of signals from the median nerve to the central parts of the brain and that there do appear to be central effects associated with carpal tunnel, as well as these peripheral effects.

So that gave us some reason to believe that if acupuncture were to have a therapeutic effect in carpal tunnel, as someone suggested, that we might be able to see that effect not looking peripherally, but looking centrally within the brain.

So he proceeded to do a clinical treatment study, several weeks of acupuncture treatments. And indeed, using conventional metrics, behavioral metrics of therapeutic response to the treatment showed that during the course of the acupuncture treatment, there was a drop in the symptom severity scale, the so-called Boston Carpal Tunnel Syndrome Questionnaire. Similarly, there was a quantitative increase in grip strength following acupuncture treatment relative to the midpoint of treatment and relative to stability in normal control subjects.

What was also nice, of course, in these subjects is that we could have a quantitative measure of what was happening within the peripheral nervous system through the measurement of median nerve latency and again, a very nice, very significant drop in latency, not down to normal levels, but moving in that direction, following several weeks of acupuncture treatment relative to pretreatment conditions.

So now the question is were there any fundamental brain effects that related to these behavioral effects that could be observed. For this, Vitali performed a simple stimulation task where he individually stimulated several of the digits in the finger, both to look at the distribution of activity and to see the relationship between the areas stimulated among the different digits, for indeed, there were some suggestions that some of the abnormalities were related to, if you will, a blurring of the distinction between the digits.

Indeed, when you look at healthy controls, you see this kind of very typical pattern now, been documented with both PET and MRI for many, many years, increased signal within the primary somatosensory cortex on the contralateral side, ipsilateral to the stimulation because of course the brain switches sides on us. We actually see areas of decreased activity within those same parts of the brain during normal stimulation of the digits.

Look at the patients with the carpal tunnel syndrome, however. This again is at baseline. They also show this activation, but in general, showed much more robust activity in the face of the same stimulus relative to the normal controls and interestingly, a lack of this drop in signal on the contralateral side, suggesting a generalized and bilateral disinhibition associated with the carpal tunnel syndrome, already an interesting insight as to the potential underlying neurobiology of carpal tunnel.

Now look pre- and post-acupuncture. Here we are at baseline, the same images that I showed before. Now after several weeks of the acupuncture treatment, notice that again, we still see activation, but with a pattern that's much more like what we saw in the normal subjects, more modest activation, less in the primary motor, of course, than in the sensory cortex, and interestingly enough, apparently an increase in this inhibition that we see on the contralateral side, suggesting that acupuncture has had some role in modulating this disinhibition that the carpal tunnel somehow started.

Here, we can just look at the comparison that he had between the individual digits. Interestingly enough on the healthy subjects, here is now test reliability of the ability to see activations of Digits 2, 3 and 5. You can see when he repeated the study five weeks later, he got almost the identical spots within the cortex. Look at the carpal tunnel at baseline, this merging or blending of the areas.

So not only was there a kind of more generalized increased activity, but the center of masses of the distinct digits began to blur together. Yet, after acupuncture, not only was there a drop in signal, but there seemed to be a return of that signal to a more normal distribution, as if the plastic changes that occurred during the carpal tunnel were somehow being ameliorated through the effects of the acupuncture.

So the conclusions of this very preliminary study, for indeed, there were several important controls that were not performed as part of this initial pilot study, was that we can, in fact, of course see the changes in carpal tunnel and this blurring of the digits. We saw significant improvements behaviorally with acupuncture, but we also saw corresponding changes that appeared to push the brain towards a more normal state centrally within the brain that seemed to correspond to these behavioral changes that we saw following acupuncture.

Well, so what does this make us think about and does it give us any insight, these data, into how acupuncture might benefit carpal tunnel? Well, while it gains some insight, I think it still leaves as many interesting hypotheses to be tested in the future, as it may answer questions. There are still several potential mechanisms by which acupuncture might be affecting such central changes.

It may be acting peripherally and yet, then through, kind of mechanisms of the Hebbian plasticity, those peripheral changes may be manifesting themselves centrally or perhaps through this modulation of homeostatic mechanisms within the limbic system may be acting centrally within the brain directly and perhaps some element of those central changes may then be acting peripherally. So from the top down, if you will, acting through, for example, through the cholinergic anti-inflammatory reflex.

Interesting questions, approachable with science. You might imagine if central mechanisms are key, then acupuncture to distant sites may have similar effects. Whereas, if the local effects of acupuncture, perhaps an increase in blood flow due to acupuncture right near the site of the injury were to be key, then you would expect much larger changes with local acupuncture than, say, on the contralateral side, important studies that we're now in a position to be able to perform with quantitative metrics.

All of these kinds of data also lead to questions of what may be happening more broadly in the brain in a modulatory sense during acupuncture and perhaps why

acupuncture may have, as some practitioners believe, greater effects in abnormal states than, say, in normal conditions.

For this, I'll highlight some very interesting data using the pharmacologic MR technique originally described by Bruce Jenkins and studies performed by Iris Chen, who's been doing the rodent work.

Here, she created a transient abnormality, a very dramatic one, within the dopaminergic system through the infusion of a powerful pharmacologic agent, amphetamine, which is known to induce a large release of dopamine. And in fact, you can see this broad effect on the underlying hemodynamics following an amphetamine injection.

Her question was, however, would acupuncture actually modulate the effects of amphetamine directly on the brain. And indeed, you can see in the time course of signal changes following the amphetamine this rapid increase in signal turn on in this case electrical four pulse stimulation, the animal analog, the homologue of acupuncture, and you can see almost immediately that the signal characteristics change and seem to return to a baseline condition more rapidly than the normal kinetic washout of the amphetamine and its effects.

Of course, we were interested to see whether this was related to perhaps some generalized hemodynamic effect or was really directly related to the dopaminergic system in animals. Of course, we're able to perform microdialysis to directly measure dopamine and so here, we're actually comparing the MR signal. This is without acupuncture, this is with acupuncture.

Here, with microdialysis where we directly measure dopamine levels within the striatum, we can see increases and a slow return to baseline without acupuncture. With acupuncture, a corresponding drop in intracellular dopamine levels, modulated by the acupuncture specifically that modulates that part of the brain and that particular neurotransmitter system directly and as you can see, literally within just a few minutes.

Iris has now begun to extend this to look at other neurotransmitters and in fact, sees that with acupuncture stimulation relative to the changes with the amphetamine alone, rather modest changes with amphetamine alone than with GABA, but much more dramatic changes when the amphetamine is combined with electrical stimulation. And

the same seems to be true of glutamate, some increase in glutamate with amphetamine, even larger increases with acupuncture.

So again, if you will, the yin and the yang, some neurotransmitters are being inhibited following acupunctures, others seemingly boosted in the setting where there's an underlying perturbation in the neurotransmitter system.

And this has allowed her to begin to think about how these neurotransmitter interactions may explain the kind of broader effects of the acupuncture and how it may be that acupuncture may exert larger effects in our patients that have perturbations in underlying neurosystems than in healthy subjects.

And she's even begun to try to tease out a model for the connections between these neurotransmitter systems and how they ultimately may work together in order to modulate key brain regions and key limbic structures through their interactions.