



## Efficacy of Acupuncture Treatment to Improve Cognitive Function in a Brain Injury Patient: A Case Study

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### Abstract

This case study explored the relationship between acupuncture and cognitive therapy with cognition and neural function following TBI. Outcome measures were the Rivermead Behavioral Memory Test (RBMT), Wisconsin Card Sorting Test (WCST) and fMRI. Results revealed improvements on the RBMT and WCST from baseline to endpoint that were maintained at follow-up. fMRI showed small clusters of activation at baseline with more widespread activation at end point. Activation decreased at follow-up but remained stronger than baseline. Acupuncture with cognitive therapy may have improved cognition in this case. Future research should address acupuncture plus cognitive therapy using larger samples and randomized control design.

**Keywords:** Acupuncture; Brain injury; Functional neuroimaging; Cognition; fMRI

### Introduction

Acupuncture has been part of Chinese health care for thousands of years and was introduced in the U.S. in 1972. Acupuncture is practiced for relief or prevention of pain and various health conditions [1]. According to the 2002 National Health Interview Survey of complementary and alternative medicine 8.2 million U.S. adults were using acupuncture at the time and 2.1 million U.S. adults used acupuncture in the previous year [2].

Acupuncture, as a medical intervention, is based on the premise that there are patterns of energy flow (Qi; pronounced “Chee”) through the body and these Qi are essential for health. Disruptions of this flow are believed to be responsible for disease. Acupuncture theoretically corrects imbalances of energy flow [3,4].

Acupuncture has become more widely used in recent years and is becoming a more common complement to traditional therapies [5]. However, there is limited evidence acupuncture is effective for treating cognitive disorders following neurological injury. In a meta-analysis of four clinical trials (n = 368) the overall estimate regarding neurological functioning suggested the odds of improvement in global neurological deficit was higher in the acupuncture group compared with the control group (odds ratio = 6.55) [6]. A more recent meta-analysis targeting acupuncture as a treatment for cognitive impairment following stroke included 21 trials and 1,421 patients. The conclusions were that acupuncture may have a positive effect on cognitive function [7]. Additionally, a single study of 20 adults incurring Traumatic Brain Injuries (TBI) two to three years prior to study enrollment, functioning at a Rancho level V (Confused, Inappropriate, Non-Agitated-Maximal Assistance) or better and randomized to acupuncture or control was published. While the study was not designed to address the question of cognitive gains directly related to acupuncture, the evidence of improved cognitive test performance for the acupuncture group suggests a possible relationship between cognitive gain and acupuncture [8]. The available literature shows promise for acupuncture as a treatment for cognitive disorders, however, more evidence is needed to determine the benefit of acupuncture for cognitive impairments specifically related to Traumatic Brain Injury (TBI). Given mechanistic, epidemiologic and cognitive sequelae differences between stroke and TBI, evidence of effect of acupuncture on cognition after TBI is warranted [9].

The purpose of this case study was to explore the potential relationship between acupuncture in conjunction with cognitive therapy and changes in cognition for a person experiencing persisting

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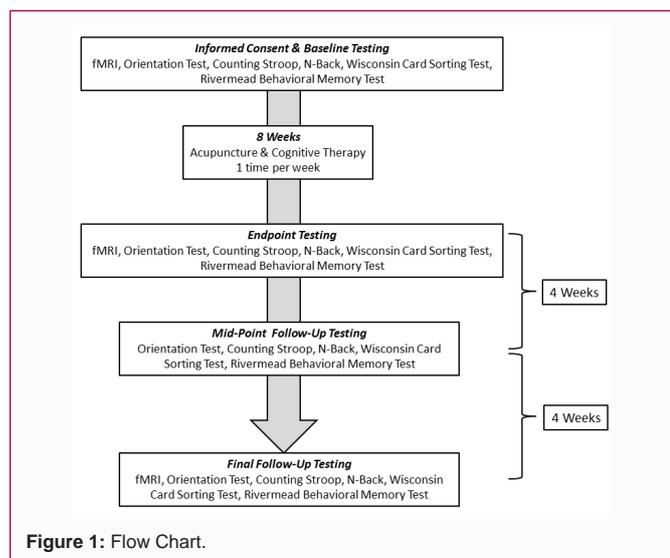


Figure 1: Flow Chart.

cognitive impairments due to a TBI. The secondary purpose was to explore the possible relationship between acupuncture with cognitive therapy and changes in activation volume in the bilateral temporal areas, anterior cingulate cortex and/or the right pre-frontal dorsolateral area as shown by functional neuroimaging measures.

## Case Description

### Research participant

The participant was a 39 year old, Caucasian, English speaking male who sustained a TBI at the age of 28. Cause of injury was a high-speed motor vehicle accident where he was a restrained front seat passenger. At time of injury, the participant had a Glasgow Coma Scale score of 3 indicating severe TBI. CT scan of the brain revealed right cerebral edema with hemorrhage extending into the third and fourth ventricles. At time of study participation, 11 years post-injury, this high school educated, unmarried gentleman was unemployed receiving disability benefits. He was at a Rancho Los Amigos Cognitive Level VII characterized by the ability to perform daily activities, slower than normal rates of carry-over for new learning and impaired judgement. No rehabilitation services were being provided at study enrollment nor during study participation. There was no pre-injury history of learning disabilities or mental health disorders.

### Study design

This research participant received weekly acupuncture sessions lasting 30 minutes followed by one hour of cognitive therapy over eight weeks. Treatment effects were measured via performance on cognitive tests and functional magnetic resonance imaging (fMRI).

Table 1: Description and Rationale for Chosen Acupuncture Points.

Acupuncture Point	Location on Body	Disturbance/Rationale for Point
Gall Bladder 39 (GB-39)	Above the tip of the external malleolus	Emotional issues
Heart 7 (H7)	Wrist crease on radial side of flexor carpi ulnaris tendon	Emotional issues with related sleep or thinking problems
Spleen 6 (SP6)	Above the medial malleolus on posterior border of tibia	Anxiety related emotions
Master of Heart (MH6/PC6)	Above wrist crease on radial side of flexor carpi ulnaris tendon	Emotional disturbances
Stomach 36 (ST36)	One finger width lateral from the anterior border of the tibia	Psychological and emotional disorders
Large Intestine 4 (Li4)	Middle of the 2 <sup>nd</sup> metacarpal bone on the radial side	Headaches
Triple Heater 8 (TH8)	Between the radius and ulna	Aphasia
Spiritual (GV20)	At the top, midline of head	Association areas for memory and behavior

These measures were completed at baseline, at end of the Eight-Week Treatment (Endpoint), and two times during an eight-week wash-out phase (at four weeks – mid-point follow-up and eight weeks – final follow-up). At final follow-up study participation was complete (Figure 1).

The acupuncture, cognitive therapy and cognitive testing were conducted at an acute rehabilitation hospital in the Midwest region of the U.S. Neuroimaging was conducted at an imaging facility affiliated with a large, urban acute care hospital and university. Informed consent was obtained from the participant prior to engaging in study procedures. Institutional Review Board approvals were obtained at both participation sites prior to subject recruitment.

### Acupuncture procedures

Each acupuncture session involved manual acupuncture at eight points. Acupuncture sessions were conducted by a licensed and certified physician/acupuncturist in an outpatient medical clinic. Seisin #5 acupuncture needles were used. The depth of penetration in the skin/subcutaneous locations was 1 to 2 mm. Table 1 provides location and description of these points. The eight points were Gall Bladder 39 (GB-39), Heart 7(H7), Spleen 6 (SP6), Master of Heart (MH6 or PC6), Stomach 36 (ST36), Large Intestine 4 (Li4), Triple Heaters 8 (TH8) and Spiritual (GV20). All points have theorized relationships to the brain and cognitive functions such as orientation, impulsivity, short term memory, attention, executive function, categorization and agitation in addition to other physical, mental and emotional symptoms (e.g., headaches, quality of life).

### Cognitive treatment description

A standardized cognitive therapy program was provided by a licensed speech-language pathologist. Each individualized session addressed six cognitive domains: orientation, short term memory, shifting attention, directed attention, categorization, and executive functioning.

### Repeated measures assessment battery

A cognitive testing battery was administered at four time points. The tests were selected to measure orientation, memory, attention, executive function and quality of life. All tests were administered by a licensed speech-language pathologist with experience in administration of standardized tests. For repeated tests, alternate forms were used when available. the tests included were as follows:

- Galveston Orientation Amnesia Test (GOAT), which examines orientation to time, place and person and is a valid and reliable measure of post traumatic amnesia [10,11].
- Rivermead Behavioral Memory Test-3 (RBMT-3), which was developed as an ecologically valid assessment of everyday memory

skills in persons with brain injury [12]. This version of the RBMT has been shown to be a reliable and valid measure of memory skills [12]. RBMT-3 is comprised of 14 sub-tests that assess the domains of verbal memory, visual memory, spatial memory, prospective memory, orientation and new learning. Raw scores range from 4 - 51 points and are converted to a scaled score of 1-19 with a mean of 10 (SD = 3) [12]. The General Memory Index (GMI) is an overall score obtained by converting the summed subtest scaled scores to a standardized score with a mean of 100 (SD = 15).

- Wisconsin Card Sorting Test (WCST), which examines executive function through requirements of planning, organization, use of environmental feedback to shift cognitive sets and regulating impulsive responses [13].

Participants are provided with a stack of cards and asked to match the cards while the test administrator tells the patient if their matches were correct or incorrect. The participant must determine the sorting rules based on the administrator's responses which shift throughout the test. Scores are generated with regard to number of categories achieved, number of trials completed, number of errors and number of perseverative errors [14].

- Satisfaction with Life Scale (SWLS) is a five item self-rated questionnaire on a Likert scale and measures global life satisfaction [15].

### Functional neuroimaging methods

Functional images were acquired on a Siemens 3T Tim Trio scanner with a 12-channel head coil. The Counting Stroop task was acquired using the following parameters: repetition time = 2200 ms, echo time = 20 ms, flip angle = 80, 159 slices, field of view = 896 x 812, and acquisition voxel size = 1.7 mm x 1.7 mm x 3 mm. Scan duration was approximately six minutes. A T1-weighted anatomical image was also acquired for registration purposes using a 3D magnetization-prepared rapid gradient-echo sequence (repetition time = 2300 ms; echo time = 2.97 ms; inversion time = 900 ms; flip angle = 9; 176 slices; 1 mm x 1 mm x 1 mm voxel resolution; field of view = 256 mm). The participant was instructed to remain as still as possible during scans.

The Counting Stroop task examines task directed attention and provides insight into cognitive effects experienced as a result of attention fatigue [16]. The task is also a measure of cognitive control. The Counting Stroop is a block design with a total of nine blocks; four are interference blocks and five are neutral blocks. Neutral-word control trials contained single semantic category common animals (e.g. 'dog' written three times), while interference trials contained number words that were incongruent with the correct responses (e.g., 'two' written four times). A total of 16 items were in each block. Each item was presented for a maximum of two seconds or until the participant responded. The inter-stimulus interval was two seconds. During this task, the participant was instructed to respond by pushing a button (one to four) to indicate the number of words on the screen for each item, regardless of word meaning.

Neuroimaging data was preprocessed within Statistical Parametric Mapping (SPM8) toolbox. Data were realigned to the first functional image, coregistered, normalized to MNI space and spatially smoothed (full width at half maximum = 8 mm x 8 mm x 8 mm). The first five images were discarded to allow for gradient stabilization. The T1 MPRAGE volume was processed using voxel-based morphometry. A general linear model was created using a first

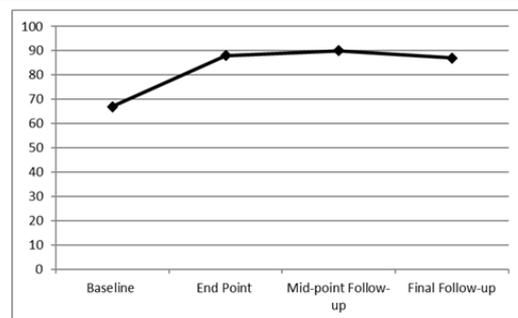
level design. Motion was regressed out of the data using the framewise displacement (FD < 1.0 mm) as a cut-off [17]. T-maps were generated to look at Interference-Neutral, Neutral-Interference and Interference + Neutral conjunction contrasts. Small volume correction was applied to the activation data at  $p < .05$  uncorrected using a mask that contained 26 regions of interest and setting the voxel extent to five. Of the 26 ROIs, 23 were extracted from the Harvard-Oxford atlas from Functional MRI Software Library (FSL) [18-20]. The other three ROIs (bilateral hippocampi and right dorsolateral prefrontal cortex (RDLPFC)) were drawn by hand onto the anatomical T1 and resliced to the functional data. These three ROIs were not available in the atlas for extraction. The 23 ROIs extracted from the atlas included the: Anterior Cingulate Cortex (ACC), left and right anterior, posterior and temporal-occipital Inferior Temporal Lobes (ITL), left and right anterior and posterior Superior Temporal Lobes (STL), left and right anterior, posterior and temporal-occipital Medial Temporal Lobes (MTL), and left and right Heschl's regions.

## Results

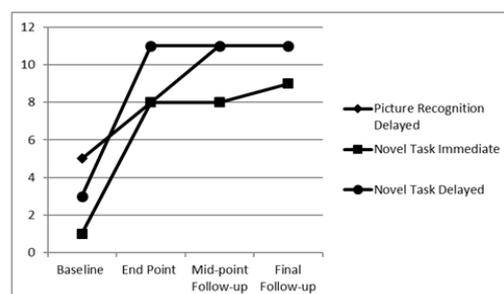
### Cognitive testing

There were no meaningful changes in orientation. GOAT scores remained stable from baseline (14/16) to final follow-up (16/16) indicating the patient maintained emergence from Post-Traumatic Amnesia throughout study participation.

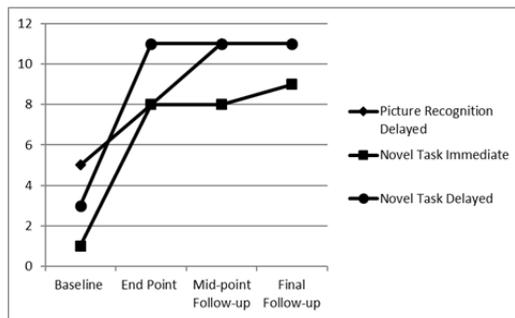
Results from the RBMT-3 are illustrated in Figures 2 and 3. Figure 2 illustrates the improved GMI test performance between baseline (GMI = 67) and endpoint (GMI = 88) with maintenance of this improvement through the follow-up (GMI = 87). Examination of specific subtest scores of the RBMT-3 revealed improvements of at least 1 standard deviation (SD = 3) on the subtests of Picture-Recognition Delayed, Novel Task Immediate and Novel Task Delayed



**Figure 2:** Rivermead Behavioral Memory Test. General Memory Index results.



**Figure 3:** Rivermead behavioral memory test results. Scores for immediate and delayed novel task and delayed picture recognition.



**Figure 4:** Wisconsin Card Sorting Test Results. Scores for novel task immediate and delayed and delayed picture recognition.

(Figure 3).

WCST results are provided in Figure 4. WCST standard scores at baseline were in the range of mild-moderate impairment (number of errors = 74, % perseverative errors = 77 and non-perseverative errors = 74) and mild impairment (perseverative responses = 81, perseverative errors = 77), which improved at endpoint to mild impairment (number of errors = 82) or average performance (perseverative responses = 93, percent perseverative responses = 96, perseverative errors = 92). This improvement was maintained at the final follow-up. Number of correct trials improved from 72 at baseline to 85 at endpoint, which declined to 80 at final follow-up.

Scores on the SWLS did not show meaningful changes. Baseline score of 12 remained stable at the mid-point and final follow-up with scores of 13 and 12 respectively. There was a considerable decline to 5 at the endpoint, however, the participant had received some troubling news just prior to completing the SWLS. Scores in the range of 10-14 are classified as dissatisfied with life [21].

### Functional neuroimaging

When comparing all interference blocks with all neutral blocks, activation at baseline was seen in the left inferior and medial temporal lobes and the right medial temporal lobe (Figure 5). At endpoint (Figure 5) activation was seen in the right motor cortex, left inferior and medial temporal lobes, right superior temporal lobe and the left hippocampus for the same contrast. At final follow-up, (Figure 5) activation was seen in the same areas as endpoint except for the right superior temporal lobe and left hippocampus. Additional activation was seen in the anterior cingulate cortex, left motor cortex, right superior parietal lobule, right inferior temporal lobe and left superior temporal lobe.

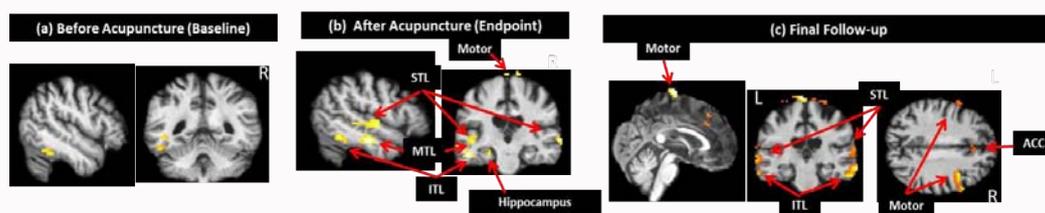
When looking at the interference and neutral blocks combined, activation in the bilateral motor cortices, bilateral superior parietal lobules and anterior cingulate cortex was seen at all three time points. The right DLPFC was activated in both conditions at baseline and end-point, but not at final follow-up. Similarly, the left hippocampus was activated in both conditions at baseline and endpoint, but not at final follow-up (Table 2).

### Discussion

The purpose of this case study was to explore the potential of acupuncture provided with cognitive therapy as a treatment to improve cognition for a person experiencing persistent cognitive impairments 11 years after TBI. Changes were measured according to cognitive test performance, behavioral performance, reported life satisfaction and changes in volume of activation with fMRI. Results show improvements in WCST scores, RBMT-3 scores and increased activation on neuroimaging measures in brain regions with key roles in learning and memory.

The WCST and RBMT-3 results indicate improved visual memory, new learning, attention and executive function temporally aligned with the provision of the treatment. Improvements were reported in memory and problem solving based on immediate and delayed performance for the novel RBMT task. This task requires the participant to recreate a design using different sized puzzle pieces. These gains between baseline and endpoint, and maintained at final follow-up, indicate improved ability to learn new information both immediately following presentation and with a delay. Reduction of trials administered on the WCST between baseline and final follow-up serve as additional evidence of improved learning, possibly supported by increased attention and executive function skills. These gains in memory, problem solving and learning are consistent with evidence from a meta-analysis of acupuncture to treat cognitive impairment following stroke [7].

Functional neuroimaging results showed increased activation in the frontal and temporal lobes. These areas are principal brain areas for learning and memory and are consistent with our aforementioned findings of improved cognitive test performance and behavioral performance. Imaging findings are also consistent with our hypothesis for increased activation immediately following acupuncture and cognitive therapy and after final follow-up. These results are also consistent with previous findings reported by Wang<sup>21</sup> who provided acupuncture at LI4 (as well as Liv3) to participants with Alzheimer's Disease or Mild Cognitive Impairment. They reported changes in activation of the frontal and temporal lobes following acupuncture [22].



**Figure 5:** Increased activation during interference blocks relative to neutral blocks. Activation at (a) baseline was absent and/or increased at (b) endpoint in the right motor cortex, left inferior (ITL) and medial temporal lobes (MTL), right superior temporal lobe (STL) and the left hippocampus. Additional activation at (c) follow-up was seen in the anterior cingulate cortex (ACC), Left motor cortex, right superior parietal lobule (not depicted), right ITL and left STL.

**Figure 5:** Increased activation during interference blocks relative to neutral blocks.

**Table 2:** Activation Regions during Counting Stroop Task.

MTL: Medial Temporal Lobe; ITL: Inferior Temporal Lobe; STL: Superior Temporal Lobe; TempOcc: Temporal Occipital Area; ACC: Anterior Cingulate Cortex; L: Left; R: Right; Ant: Anterior; Post: Posterior; Hippocamp: Hippocampus.

Contrast	BASE LINE						END POINT						FINAL FOLLOW-UP					
			Peak T-value co-ordinates (mm)			ROI			Peak T-value co-ordinates (mm)			ROI			Peak T-value co-ordinates (mm)			ROI
	# Voxels	Peak T-value	x	y	z		# Voxels	Peak T-value	x	y	z		# Voxels	Peak T-value	x	y	z	
Interference - Neutral	7	3.25	-64	-14	-8	R Post MTL	45	2.85	-50	-22	-20	L Post ITL	404	3.98	68	-28	-14	R Ant/ Post MTL
	15	2.26	70	-14	-16	R Posterior MTL	273	2.66	-64	-38	-2	L Post/ Temp Occ MTL	159	3.1	-68	-28	-4	L Post MTL & STL
	18	2.39	-50	-46	-22	L Temp Occ ITL	38	2.64	68	-8	-4	R Post STL	14	2.93	-50	-52	-20	L Temp OccITL
	9	2.09	-44	-50	-8	L Temp Occ ITL	23	2.32	62	-44	-4	R Temp Occ MTL	11	2.48	-52	-58	-20	R Temp Occ ITL
	7	1.79	56	4	-26	R Ant MTL	6	2.14	-46	-64	-16	L Temp Occ ITL	8	1.97	4	32	44	ACC
	5	2.87	68	-38	-14	L Post MTL	14	2.14	-50	-52	-16	L Temp Occ ITL	5	1.83	-2	26	32	ACC
						11	2.08	-22	-20	-20	L Hippo-camp	8	1.79	-4	14	50	ACC	
Neutral - Interference	134	3.1	-40	-40	8	L Temp Occ MTL	12	2.98	58	-62	8	R Temp Occ MTL						
	11	2.06	40	-58	2	R Temp Occ MTL	113	2.87	-34	-64	14	L Temp Occ MTL						
	15	2.06	44	-28	-20	R Post ITL	22	2.63	44	-38	-20	R Post ITL						
	10	1.82	-50	-14	2	L Heschl	16	2.5	52	4	-16	R Ant STL						
							7	2.35	64	-44	8	R Post MTL						
							5	2.21	-20	-40	2	L Hippo camp						
						23	2.21	52	-20	-4	R Post STL							
Interference + Neutral	508	4.98	-46	-64	-14	L Post/ Temp Occ MTL	1198	7.74	58	-38	-20	R Ant/ Post MTL & STL	499	4.92	-68	-44	-2	L Post/ Temp Occ MTL
	798	4.28	70	-10	-14	R Ant/ Post MTL	639	6.31	-40	-52	-4	L Temp Occ ITL	479	4.77	52	-58	-20	R Temp Occ ITL
	65	2.92	-32	-32	-8	L Hippo camp	18	3.75	-26	-38	-8	L Hippo camp	298	3.07	8	16	44	ACC
	11	2.72	52	-56	-20	R Temp Occ ITL	53	3.27	38	32	20	RDLPFC	21	2.91	-44	-40	-10	L Temp Occ ITL
	102	2.45	2	10	56	ACC	5	2.94	20	-38	2	R Hippo camp						
	63	2.39	-16	44	-4	ACC	45	2.35	14	46	32	ACC						
	15	2.32	46	-46	2	R TempOcc MTL	25	2.26	20	40	2	ACC						
	5	1.77	40	28	26	RDLPFC	10	2.05	8	52	-8	ACC						
						12	2.02	-10	28	38	ACC							

Our findings of activation changes are consistent with the literature related to brain regions showing activation during the Counting Stroop task [16]. However, our findings of changes between neutral and interference blocks are dissimilar with results for healthy people [23] where activation in regions known to comprise the cognitive/attention network (anterior cingulate cortex, right DLPFC and superior parietal lobules) [24] was seen during both interference and neutral blocks at baseline and endpoint. Our findings at final follow-up, however, indicate continued activation between the anterior cingulate cortex and the superior parietal lobules but absence of right DLPFC activation. This could indicate improved connection between these regions that are structurally connected through the

cingulum white matter fibers and are part of an attention/cognition network. A potentially improved connection between the anterior cingulate cortex and the superior parietal lobules is indicated further by WCST improvement in accuracy of responses and reduction in perseverative responses, which could be attributed to improved attention and executive function skills.

Functional activation findings for this case are also inconsistent with activation findings for healthy persons who show increased activity in the anterior cingulate cortex during Interference blocks (compared to neutral blocks) [23]. While our participant manifested activity in the anterior cingulate cortex at all three time points for the Interference and Neutral blocks separately, the increased activation in

the anterior cingulate cortex during Interference and Neutral blocks was only seen at final follow-up. This dissimilarity is also true for the right superior parietal lobule. This finding suggests the anterior cingulate cortex for this patient does not function efficiently when presented with multiple tasks and given the established role of the anterior cingulate cortex in allocating attentional resources this likely contributes to persisting cognitive impairments.

A final noteworthy result is the detected changes in hippocampal and temporal lobe activation. Bilateral medial and left inferior temporal lobe activation was identified at baseline and endpoint; with additional activation at endpoint within the right superior temporal lobe and left hippocampus. At final follow-up, activation was identified in the anterior cingulate cortex, right inferior and left superior temporal lobe. There was no hippocampal activation at baseline or final follow-up, but the left hippocampal activation at endpoint is consistent with improved RBMT memory scores at endpoint. While the activation in the hippocampus was not maintained the behavioral improvements in RBMT memory scores were maintained at final follow-up. Changes in fMRI activation and evidence of cognitive improvement with clinical cognitive testing indicate possible molecular changes that may be attributed to acupuncture. Literature from animal models showing a positive change in cognitive impairment after acupuncture point to the modulation of signaling pathways such as cholinergic and dopaminergic transmissions [25]. These cholinergic and dopaminergic pathways are well documented as pathways necessary for cognitive function [26].

Improvements in cognitive function in a patient 11 years after injury are very promising results, but this case study's generalizability to the larger TBI patient population is limited. An additional limitation is the patient's use of prescribed medications was not recorded. Repeated administration of the cognitive tests may have resulted in practice effects, but this was minimized by using alternate forms of the RBMT.

## Conclusions

For our participant, the reported findings collectively suggest acupuncture combined with cognitive therapy may have improved his cognitive test performance and behavioral performance. Furthermore, the effects of acupuncture combined with cognitive therapy may result in improved performance extending beyond the period of treatment. Improvements on the RBMT-3, WCST and increased activation in key brain regions indicate a possible relationship between improved memory, attention, executive function and neuroplasticity. Given the consistency of our findings with findings in the literature, the likelihood of a relationship between provision of acupuncture and cognitive therapy with improved cognition is further supported. Future research should focus on using acupuncture with cognitive therapy in a larger sample size and a randomized control design. Addition of functional neuroimaging techniques measuring diffusion tensor imaging or resting state functional connectivity may also be helpful to better understand the effect acupuncture is having on neuroplasticity.

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