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Quantitative EEG Markers of Post-Traumatic Stress Disorder: Baseline Observations and Impact of the Reconsolidation of Traumatic Memories (RTM) Treatment Protocol.

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Abstract:

Objective: This study evaluated how qEEG and clinical measures (PCL and PSSI) from subjects with PTSD were modulated by treatment through the Reconsolidation of Traumatic Memories (RTM) protocol. RTM uses a dissociative reimaging procedure that renders reconsolidated memories of the trauma to be less emotionally impactful and intrusive.

Methods: Twelve PTSD subjects underwent qEEG and clinical assessments at baseline and 1 month after three 90-minute RTM treatment sessions (administered over the course of 1 week). Ten additional PTSD subjects were evaluated at baseline and 1-month following a no-treatment waiting period. qEEG data were evaluated with respect to a normative database. Baseline EEG data were also evaluated from twenty-two age and sex matched neurotypical control subjects.

Results: At baseline, only 3/22 control subjects showed some elevation in high-beta activity. In contrast, 15/22 PTSD subjects showed excessive power in the high-beta range. Waitlist PTSD subjects showed minimal clinical or EEG changes between baseline and follow-up evaluations, whereas RTM subjects showed highly significant ($p<0.001$) reductions in PCL and PSSI scores, along with normalization of excessive high-beta activity. Source modelling using the LORETA algorithm showed that the baseline abnormalities in high-beta were mostly generated in mesial temporal (hippocampus and amygdala), insular, frontal, and parietal regions. Post-treatment normalization mostly reflected changes in mesial temporal areas.

Conclusions: High-beta activity may be a useful biomarker of PTSD that can be used to objectively track the neurobiological impact of behavioral therapies. The RTM protocol appears to be efficacious in reducing the clinical symptoms of PTSD and in normalizing brain activity.

Introduction:

Post-Traumatic Stress Disorder (PTSD) is a potentially debilitating disorder that is triggered by exposure to a significantly stressful traumatic event threatening death or physical injury to oneself or others. Core features of PTSD include intrusive re-experiencing (nightmares and flashbacks), avoidance, negative cognition and mood, and disturbances in arousal and reactivity [1]. Available data indicate the lifetime prevalence of PTSD among adult Americans to be just below 8% [2].

Multiple treatment approaches are used for PTSD, including pharmacotherapy and a range of cognitive and behavioral approaches including exposure therapy, cognitive processing therapy, mindfulness and EMDR (eye movement desensitization and reprocessing) therapy. Available data suggest that these various approaches generally provide significant relief of PTSD symptoms in only 25-50% of patients [3-5]. These approaches can also be expensive and time-intensive, with most cognitive-behavioral interventions requiring 15-30+ therapeutic sessions.

Given the current situation, there is mounting hope that a better understanding of the neurobiology of PTSD will lead to the development of better and more efficient therapies [6]. Several lines of human and animal research data converge to demonstrate PTSD-related changes in brain structure and function. Of particular note are reductions in the volume of the hippocampus and ventromedial prefrontal cortex, and increased activity in the amygdala [7-9]. These brain regions are key nodes in brain networks that support the processing of emotional memories. Indeed, PTSD is sometimes considered as a memory disorder in which fear responses over-generalize and fail to habituate because of disrupted memory consolidation and/or reconsolidation mechanisms [10-11]. Recent neuroscience research shows that the retrieval of memories under certain conditions can open a 1-6 hour window during which reactivated memories can be updated and modified, or even erased [12-16]. This transient process, known as reconsolidation, may have important implications for PTSD treatment [17-18].

These data on mnemonic processing in PTSD have helped to motivate a new treatment approach to PTSD – the Reconsolidation of Traumatic Memories Protocol (RTM) [19-22]. RTM is a cognitive behavioral therapy that explicitly targets the intrusive symptoms of PTSD experienced as sudden and uncontrollable autonomic (sympathetic) responses to the trauma narrative, its elements, or the triggers for flashbacks and nightmares. RTM begins with a brief, quickly terminated recall of the traumatic event that is believed to 'open' the reconsolidation window. The protocol then takes the client through a series of dissociative and perception-modifying visual imagery exercises that are believed to restructure the traumatic memory, especially in relationship to persistent and pathological emotional responses. Typically, this protocol is completed over the course of three to five 90-minute long sessions administered over a 5-10 day window.

Anecdotal reports, published case series, and a published peer-reviewed wait-list control study all indicate that the RTM protocol is remarkably effective at reducing PTSD symptoms for >80% of treated clients [19-22]. For example, in a study of 30 male veterans with PTSD [19], 26 completed the protocol with a mean treatment-related reduction in PTSD symptoms of 33 points as measured at six-weeks post treatment by the PTSD Symptom Checklist Military Version (PCL-M). Given the rapid, medication-free nature of the RTM protocol, the method holds great promise for changing the current landscape of PTSD treatment strategies. In considering this, there is general recognition that clinical evaluations of RTM and other PTSD treatment strategies would benefit from a reliable, easily evaluated and objective biomarker for PTSD.

Prior research has demonstrated PTSD-related alterations in data derived from MRI, Positron Emission Tomography (PET), electroencephalography (EEG) and magnetoencephalography (MEG) methods [7-9, 23-27]. Unfortunately, most of these methods and extracted biomarkers have substantial practical limitations. For example, PET and various types of MRI (structural, functional, DTI, spectroscopy) readily show group differences between PTSD and control subjects, but these measures fail as input variables for accurate classification of individual subjects as belonging to PTSD versus control groups. A viable biomarker for clinical studies must be successfully applicable at the individual subject level. Other limitations include the

need for radiation (PET), limited availability (MEG), and/or high cost (>$2000, MRI, PET, MEG). In contrast to the other methods, EEG offers an especially attractive profile with respect to PTSD studies. The method is inexpensive, portable, essentially risk-free and patient friendly, with commercially available normative databases and software for extraction of quantitative metrics and statistical evaluations that provide viable information on how an individual subject deviates from a control population. Given this, the present study sought to (1) identify quantitative EEG (qEEG) metrics for PTSD, and (2) to explore how treatment via the RTM protocol impacts these metrics and clinical symptom severity.

Methods:

Overview of Study Design:

The study was designed as a waitlist controlled evaluation of the impact of the Reconsolidation of Traumatic Memories (RTM) treatment protocol on the clinical symptoms of PTSD and PTSD-related quantitative EEG biomarkers. Clinical and qEEG data were collected at baseline and 4 weeks following 1 week (active treatment group, 3 sessions total) of RTM treatment or no intervention (waitlist group). Subjects and clinical evaluators were aware of treatment assignments (active versus waitlist), but qEEG data were processed in the absence of this information.

Subjects:

PTSD specific clinical data and qEEG data were newly collected and analyzed from 25 subjects with a diagnosis of PTSD. The group consisted of 18 males and 7 females, ranging in age from 27-74 years. Inclusion criteria were a medical diagnosis of PTSD, a baseline score above 20 points on the post-traumatic stress disorder symptom interview (PSSI) [28], a baseline score on the post-traumatic stress disorder symptom checklist (PCL) [29] above 50 points for combat related PTSD or 40 points for non-service related PTSD, and clinical

evidence of sympathetic physiological arousal (flushing, sweating, rapid breathing, etc.) while briefly recounting traumatic events. In all cases, significant symptoms had been present for at least 12 months. The presence of traumatic brain injury or associated depression was not considered exclusionary, as these are very common real-world co-morbidities for PTSD, especially in military populations. A current substance use disorder and other axis I psychiatric disorders were considered exclusionary. All subjects signed an IRB approved consent form describing the study, prior to any assessments other than a brief phone screen.

For comparison purposes, previously collected qEEG data from 25 sex and age-matched (within 2 years) case-control neurotypical subjects were drawn and analyzed from a larger normative database (N=82). Each of these subjects was free of any neurological or psychiatric diagnoses, learning or developmental disabilities, or history of substance abuse.

Baseline Assessment of PTSD Symptoms:

Clinical symptoms of PTSD were assessed and documented through completion of a clinical interview -- the PSSI, and a self-report symptom checklist -- the PCL (military or civilian versions, as appropriate). Each subject was also asked about the frequency of intrusive symptoms (nightmares and flashbacks) over the one month period preceding evaluation. A record was made of all medications.

Baseline Quantitative EEG Data Acquisition and Analyses:

Fifteen minutes of eyes closed resting state data were collected using a 21-channel electrode array (International 10-20 system, including left and right mastoids). Data were collected with a left-ear referential montage, with subsequent digital re-referencing to linked-mastoids. Individual electrode impedances were maintained below 10 KOhms. The data stream was digitized at 256 Hz. Quantitative analyses were performed using the NeuroGuide software suite (Applied Neuroscience Inc. Largo, FL). As a pre-processing step, the

NeuroGuide automated pipeline for selection of time windows without evidence of eye artifacts, drowsiness, and muscle artifacts was run, all with settings at 'very high', indicating the strictest of criteria for selection of 'clean' artifact free data segments .

Using only the clean data, the NeuroGuide software calculated the absolute and relative power for delta (1-4 Hz), theta (4-8 Hz), alpha (8-12 Hz) , beta (12-25 Hz), high-beta (25-30 Hz) and gamma bands (30-40 and 40-50 Hz), plus additional measures of inter-electrode relationships (phase-lag index, amplitude asymmetry, and coherence). NeuroGuide has a built-in normative database of over 600 subjects across the lifespan. Z-scores were calculated for each subject metric using an age and sex corrected regression model.

At one week and one month post-treatment time-points, the PSSI was completed with respect to the total time that had elapsed since treatment, with a focus on symptoms only related to the traumatic events treated during RTM sessions. The PCL was also completed, but this was done with respect to each subject's overall trauma history (that is, without restriction to just RTM treated traumatic events).

RTM Treatment:

Fourteen subjects were assigned to the active treatment group, with eleven subjects forming the waitlist control group. RTM treatment was implemented across three 90-minute treatment sessions completed during a one week window, as administered by a trained clinician affiliated with the Research Recognition Project (http://nlprandr.org) where the RTM protocol was developed. Most subjects in this study had multiple traumatic events. Initial treatment focused on each subject's self-identified most distressing event.

The key steps in the RMT treatment protocol [19-22] are provided in Table1, with additional information on memory modification strategies provided in the Supplementary Materials. Briefly, each session began with a quickly terminated recall of the traumatic event, this intended to reactivate the memory and open the reconsolidation window. Through a series of guided dissociative visual imagery exercises, the client engaged in

perceptual manipulation of the traumatic memory (e.g., recalling the event from a third person perspective, viewing it in black and white, in reverse order, and at high speed) in a manner that ultimately allows for recall of the event without triggering emotional hyperarousal. If the protocol for the main traumatic event was completed in fewer than three sessions, additional events were treated, in order of severity. In several cases, 2-3 separate traumatic events were treated.

Table 1: Detailed Step-by-Step Description of the RTM Process

1. The client is asked to briefly recount the trauma.
2. Their narrative *is terminated as soon as autonomic arousal is observed*. – steps 1 and 2 are believed to open the reconsolidation window.
3. The subject is reoriented to the present time and circumstances.
4. SUDs (subjective units of distress) ratings are elicited.
5. The clinician assists the client in choosing times before and after the event (bookends) as delimiters for the event: one before they knew the event would occur and another when they knew that the specific event was over and that they had survived.
6. The client is guided through the construction (or recall) of an imaginal movie theater in which the pre-trauma bookend is displayed in black and white on the screen.
7. The client is instructed in how to find a seat in the theater, remain dissociated from the content, and alter their perception of a black and white movie of the index event.
8. A black and white movie of the event is played and is then repeated with structural alterations as needed, see Supplementary Material - 1.
9. When the client is comfortable with the black and white representation, they are invited to step into a two-second, fully-associated, reversed experience of the episode beginning with the post-trauma resource and ending with the pre-trauma resource.
10. When the client signals that the rewind was comfortable, they are probed for responses to stimuli which had previously elicited the autonomic response.
11. SUDs ratings are elicited.
12. When the client is free from emotions in retelling, or sufficiently comfortable (SUDs ≤ 3), they are invited to walk through several alternate, non-traumatizing versions of the previously traumatizing event of their own design.
13. After the new scenarios have been practiced, the client is again asked to relate the trauma narrative and his previous triggers are probed.
14. SUDs ratings are elicited.
15. When the trauma cannot be evoked and the narrative can be told without significant autonomic arousal and a SUD of only 1 or 0, the procedure for that traumatic event is over.

Table 1: Basic Step of the RTM Treatment Protocol.

Results:

Good quality EEG data were collected in all but one case (in the active treatment group)where there was excessive contamination by muscle and eye movement artifacts to the point that results could not be validly interpreted at either baseline or follow-up assessment. Although this subject was responsive to therapy, given the uninterpretable state of the EEG data, he was removed from subsequent analyses.

One subject experienced a new PTSD provoking traumatic event following active RTM but before follow-up assessment. At follow-up she demonstrated significant overall PTSD symptoms especially with respect to avoidance and arousal behaviors (baseline PCL = 74, 1-month PCL = 67). However, when asked about her symptoms exclusively with respect to the treated trauma, she reported no symptoms (1-month PCL specific = 17, baseline PSSI = 41, 1-month PSSI specific = 0). Nevertheless, given the intervening trauma, a post-hoc decision was made to remove this subject from subsequent analyses.

The treating physician of one patient in the waitlist control group initiated a protocol violation for clinical reasons, having the subject begin medication with an SSRI between the time of baseline and follow-up examinations. As such, this subject was also removed from subsequent analyses. So, data from a total of 22 study participants with PTSD (10 wait list, 12 active RTM) are considered here, along with data from the 22 case-control, age and sex matched neurotypical control subjects.

Few of the neurotypical control subjects, but essentially all of the PTSD subjects showed a substantial number of abnormal EEG metrics at baseline. However, within the PTSD group, there was little consistency in the profile of abnormalities, with the exception of z-scores for absolute high-beta power. Figure 1 (top panel) shows z-score maps for high-beta activity for the 22 neurotypical case control subjects, as compared to the NeuroGuide normative database. High-beta maps for these subjects did not show deviations from the normative

database beyond expectations, an indication of the veracity of the database approach (Maps are shown with a threshold of +/- 1 standard deviation, so it is expected that 16% of subjects {that is, 3-4 subjects} would show values greater than 1 standard deviation above the mean, and that 16% of subjects would show values more than 1 standard deviation below the mean).

Figure 1 (bottom panel) shows the comparable maps for the 22 PTSD subjects. Fifteen (68%) of the PTSD subjects showed evidence of increased high-beta activity relative to the normative database, whereas only 3-4 subject are expected to show such deviation based on chance. Within the PTSD group, there was not a significant relationship between the extent of beta abnormality and baseline symptom severity. In comparison to the neurotypical control group, the rate of elevated high-beta is significantly higher in the PTSD group (Chi-square = 13.6, $p<0.0005$).

To better understand which brain regions contributed to the observed PTSD-related elevation in high-beta activity, group average data were processed using the low-resolution brain electromagnetic tomography algorithm (LORETA), as implemented in the NeuroGuide software suite. Briefly, LORETA is an EEG inversion method that estimates the brain's electric neuronal activity distribution (current density vector field) which gives rise to the scalp recorded EEG profile [30]. Figure 2 (upper left panel) shows that multiple brain regions are contributing to the increased high-beta activity in the PTSD group at baseline. Of particular note are contributions from the (1) anterior temporal lobes, including the hippocampal and amygdala regions, (2) insula, (3) superior parietal cortex (L>R), and (4) bilateral orbital, mesial, and lateral frontal cortices – all regions commonly considered to be part of the disrupted brain networks for PTSD.

FIGURE 1: Z-Score Maps – High-Beta Activity

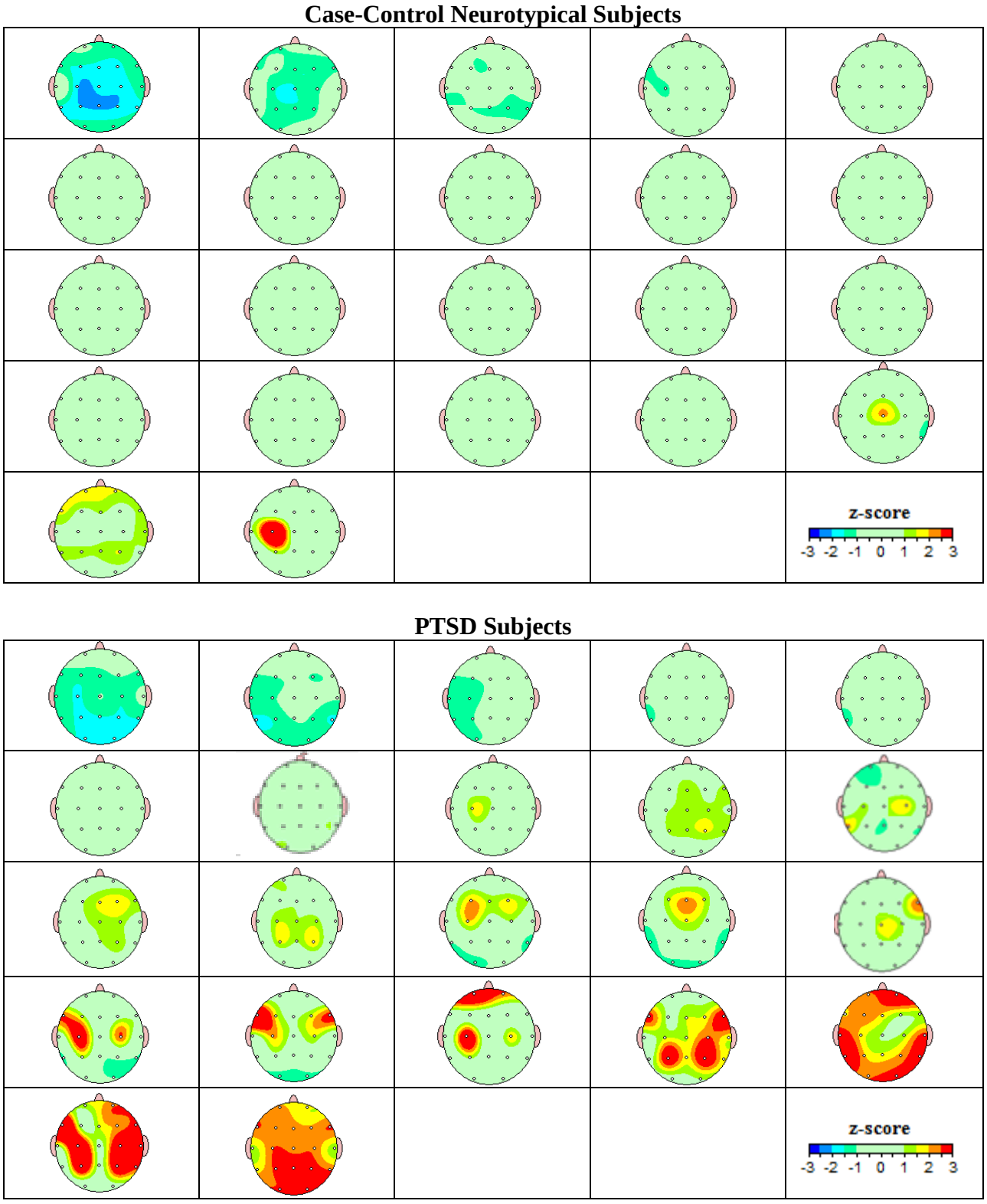


***Figure 1:** Quantitative EEG Z-score maps showing how the high-beta activity of individual subjects compares with that of the NeuroGuide normative database. Maps have a z-score threshold of z<-1, z>1. Three control subjects (14%) show elevated high-beta, whereas 16 (73%) of the PTSD subjects show elevated high-beta. This different in frequency is highly significant (Chi-square = 15.7, p<0.0001).*

Figure 2

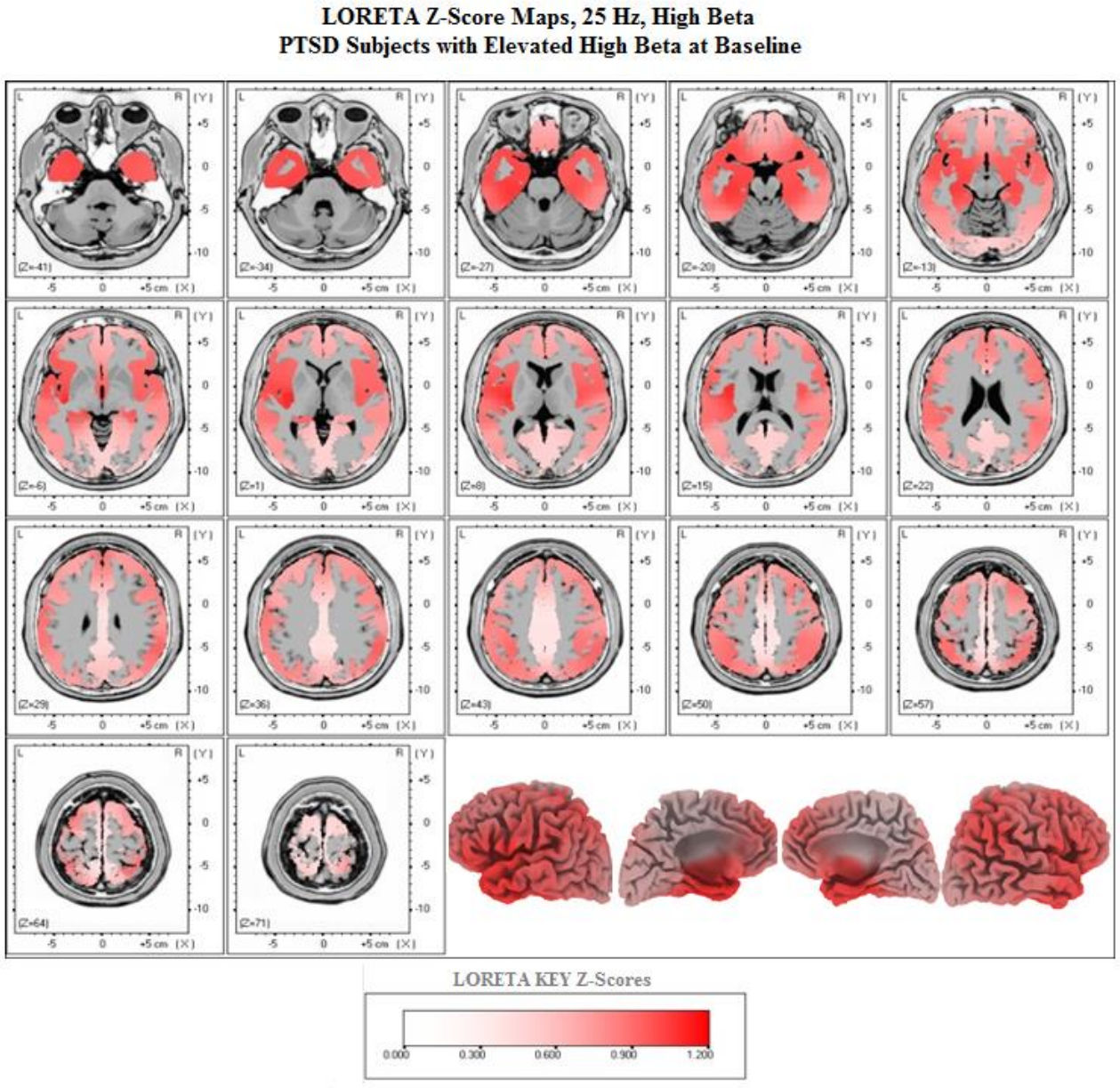


***Figure 2:** Data show group-average LORETA z-score maps for high-beta at 25 Hz for the 16 PTSD subjects with excessive high-beta activity at baseline. The maps indicate that widespread brain regions contribute to the high-beta activity, but especially anterior temporal, insula, frontal, and superior parietal regions.*

Tables 2 and 3 summarize demographic, clinical, and EEG observations on the Waitlist Control Subjects and the RTM Treated Subjects, respectively, at baseline and 1-month follow-up. When examining baseline to 1-month follow-up changes in EEG high-beta activity for subjects with excessive high-beta at baseline (N=7), three subjects (43%, WL #4, #5 and #9) showed a reduction in beta activity at follow-up (two subjects showed an increase in high-beta activity, and two showed stable profiles). In contrast, when considering RTM treated subjects with excessive high-beta at baseline (N=9), eight showed reduced high-beta at 1-month post-treatment follow up (89%, RTM #1, #3, #5, #6, #8, #9, #10, #12). This difference in the frequency of high-beta reduction between waitlist and treatment groups is significant (chi-square = 3.88, $p<0.05$).

Table 2: Demographics, Clinical and EEG Observations – Waitlist Control Subjects

id	sex	age	type	tbi	meds	PCL Base/1M	PSSI Base/1M	Intrusions Base/1M	EEG Baseline	EEG 1 Month FU
WL #1	M	40	combat	y	none	78/72	41/43	12/11		
WL #2	M	42	combat	y	none	76/62	43/42	8/8		
WL #3	M	46	natural disaster	n	Cymbalta Marijuana	73/71	42/41	22/20		
WL #4	M	43	combat	y	Prazosin Lorazepam Sertraline	71/68	27/35	10/10		
WL #5	M	54	abuse	y	none	66/41	39/21	12/8		
WL #6	M	43	combat	y	none	66/69	39/36	14/16		
WL #7	M	53	combat	y	Adderall Lorazepam Effexor	65/61	31/42	10/11		
WL #8	M	39	combat	y	Adderall Paxil	64/56	34/38	10/8		
WL #9	M	43	combat	y	Citalopram	60/60	37/30	18/17		
WL #10	M	71	combat	y	Citalopram	59/60	33/34	6/10		

Table 2: For waitlist control subjects, demographic data are provided on each subject's sex, age, type of PTSD inducing event, history of traumatic brain injury, and medications at time-of-study. Baseline (Base) and 1-month (1M) follow-up scores are provided for the PCL, PSSI, and # of intrusive events [over the prior month]. qEEG, high-beta z-score maps are also provided at baseline and 1-month follow-up. (Subjects are ordered according to baseline PCL scores). Data demonstrate that, in the absence of treatment, clinical symptoms and EEG profiles are relatively stable.

Table 3: Demographic, Clinical and EEG Observations – RTM Treated Subjects

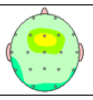
id	sex	age	type	tbi	meds	PCL Base/1M	PSSI Base/1M	Intrusions Base/1M	EEG Baseline	EEG 1 Month FU
RTM #1	F	49	first responder fire	n	Prozac Gabapentin Alprozolam	83/20	46/4	8/0		
RTM #2	M	37	combat	y	Marijuana	70/39	39/22	7/3		
RTM #3	M	40	combat	y	none	69/35	34/17	12/4		
RTM #4	M	73	combat	y	none	68/25	33/3	3/0		
RTM #5	M	27	combat	y	none	67/35	41/17	9/3		
RTM #6	F	42	medical	y	Clonidine	64/42	43/16	8/0		
RTM #7	F	61	domestic violence	y	Lorazepam Paroxetine Bupropion	64/29	39/13	30/2		
RTM #8	M	31	combat	y	Topimax Ambien Gabapentin Buspar Abilify Cymbalta	63/38	33/21	20/1		
RTM #9	M	70	combat	y	none	60/46	32/21	9/5		
RTM #10	M	33	first responder MVA	n	none	57/21	25/2	12/0		
RTM #11	M	74	combat	n	none	51/25	31/1	8/0		
RTM #12	F	48	accident	n	none	41/19	22/2	2/0		

Table 3: For subjects treated with the RTM protocol, demographic data are provided on each subject's sex, age, type of PTSD inducing event, history of traumatic brain injury, and medications at time-of-study. Baseline (Base) and 1-month (1M) follow-up scores are provided for the PCL, PSSI, and # of intrusive events [over the prior month]. qEEG, high-beta z-score maps are also provided at baseline and 1-month follow-up. (Subjects are ordered according to baseline PCL scores). Data demonstrate that, following RTM, there are significant reductions in clinical symptoms and substantial reductions in high-beta activity for those subjects with excessive high-beta at baseline.

Figure 3 shows how the pattern of current source activity for high-beta activity changes from baseline to 1-month follow-up assessments for the active RTM group, as assessed using the LORETA algorithm. For the

waitlist group, there is little change in activity. In contrast, RTM treatment results in selective reduction in the high-beta activity of mesial temporal regions, including the hippocampus, amygdala, and insula.

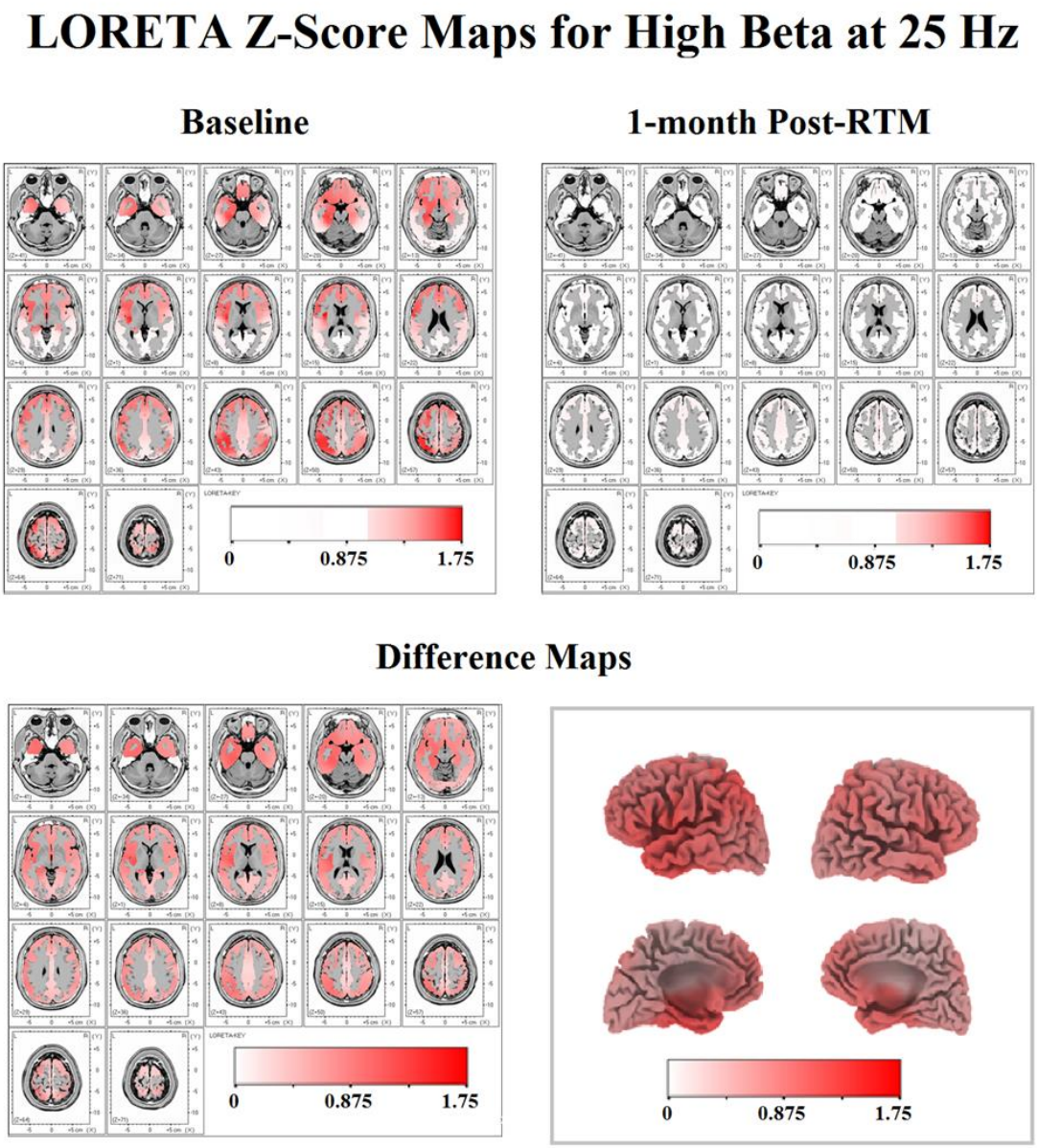


***Figure 3:** Data show group average LORETA z-score maps for high-beta at 25 Hz for the 8 PTSD subjects who had increased high-beta at baseline. Upper panels show baseline and 1-month follow-up data. The color scale ranges from z-scores of 0-1.75, but with a threshold at z > 1.0. The bottom left panel shows the difference maps, with the lower right showing corresponding 3D renderings. For the difference map, the scale still ranges from 0-1.75, but no threshold is applied. At baseline, abnormal high-beta activity is seen arising from many brain regions, but especially hippocampus and amygdala (left>right), mesial frontal regions, and the left insula and parietal lobe. At one month post RTM, maps show only minimal evidence of high-beta abnormalities. Difference maps demonstrate that the post-treatment change is associated with normalization of high-beta activity throughout the brain but especially the left mesial temporal lobe.*

Figures 4-6 illustrate the impact of the RTM protocol on critical clinical measures of PTSD severity at 1 month post-treatment (Figure 4 – PCL; Figure 5 – PSSI; Figure 6 – Intrusive Symptoms). Whereas subjects in the waitlist control group showed minimal symptom changes, treatment with the RTM protocol led to a substantial decrease in symptoms for the majority of patients. For the 10 subjects in the waitlist control group, the group average PCL score changed by less than 6 points (Figure 4); with only two subjects (WL #2 and WL #5) showing changes that are considered clinically meaningful (>10 points). In contrast, for the 12 subjects in the RTM treatment group, the group average PCL score decreased by 31 points between baseline and 1-month follow-up, with all 12 subjects showing clinically meaningful improvements. This baseline to follow-up change in PCL scores for the RTM treatment group is highly significant (t-value = 8.84, $p<0.001$) and significantly greater than that seen for the waitlist control group ($F(1,21) = 31.7$, $p<0.001$).

PSSI scores (Figure 6) also showed substantial reduction with RTM treatment, falling 23.7 points, from a baseline average of 35.3 points to only 11.6 points at 1-month follow-up (paired t-test, t-value = 9.3, $p<0.001$). For the waitlist control group, PSSI scores changed by a non-significant, 0.4 points.

The frequency of intrusive symptoms (nightmares and flashbacks) was significantly reduced by active treatment. As shown in Figure 6, for waitlist subjects there was a non-significant 2.5% change in the monthly frequency of intrusive events between baseline and 1-month follow-up evaluations (12.2 versus 11.9 events/month). In contrast, RTM treated subjects saw an 85% reduction in the frequency of intrusive symptoms (baseline = 10.7, 1-month = 1.6, t-value = 4.17, $p<0.005$).

To examine the relationship between clinical and EEG changes between baseline and follow-up evaluations each subject was assigned a global EEG change score. For each subject, this was calculated as the difference in baseline versus follow-up, average high-beta z-score across all electrodes. A regression analysis was then performed to relate changes in PCL score to this EEG change measure. The relationship was found to be significant at $p<0.05$ ($F[1,21]=4.44$), a result suggesting that change in global high-beta may be useful as a

surrogate biological marker for change in PCL score in PTSD clinical trials. Relationships between EEG high-beta change measures and changes in PSSI and intrusive symptoms were also significant at the $p<0.05$ level. However, it should be noted that there were individual cases where clinical improvement was seen in the absence of clear EEG changes (e.g., RTM #7) or even a slight worsening of the EEG (e.g., RTM #4).

Discussion:

Prior electrophysiological investigations of PTSD have suggested several potential biomarkers of PTSD, including increased theta activity [26, 31-33, but see 34 for evidence of decreased theta], frontal alpha asymmetries [35] , and increased beta activity [27, 31, 32]. The present study noted some increase in theta for some individual subjects (especially those with comorbid TBI), but this was not consistent across the full group. The present study also failed to find substantial asymmetry in frontal alpha power, but such failure has also been reported by others [33].

In the present work, PTSD related abnormalities in high-beta power were identified at both group and individual subject levels. At baseline, 15 of 22 PTSD subjects (68%) showed evidence of abnormally elevated high-beta activity. This observation of increased beta activity is consistent with several prior studies of brain electrophysiology in PTSD, including the studies of Begic and colleagues [31-32] that used methods very similar to those employed here.

Using the LORETA algorithm to explore the brain regions giving rise to increased high-beta EEG activity in PTSD, the greatest increases were observed for bilateral mesial temporal regions (hippocampus and amygdala, left > right), the insula, orbital frontal cortex and the left parietal lobe (see figure 2). The frontal and mesial temporal observations are concordant with those from a completely independent study by Huang and colleagues using MEG [27]. Huang and colleagues found their PTSD group (n=25) to show significantly elevated beta activity arising from several brain regions, with greatest increases seen for bilateral amygdala, left hippocampus, and bilateral posterior lateral orbital frontal cortex. Our data, and those of others [27, 31, 32], thereby

converge to show increased beta activity in PTSD, especially in mesial temporal and frontal brain regions (although not all studies have seen increased beta activity in PTSD [26, 33]).

Following clinical intervention with the RTM protocol, 100% of treated subjects showed clinically meaningful reductions in PTSD symptoms at one month follow-up, with 25% of subjects becoming nearly or completely symptom free. Overall, intrusive symptoms were most impacted by the RTM treatment, but coincident alleviation of avoidance, arousal, and even cognitive problems was seen for the majority of subjects. In contrast, only two (20%) of the waitlist control subjects showed clinically meaningful improvements at 1-month follow-up, and both still experienced significant symptoms.

RTM treatment also had a profound impact on brain electrophysiology, and to the best of our knowledge, the present study is the first to demonstrate that a medication-free cognitive behavioral therapeutic approach to PTSD can lead to normalization of relevant aberrant brain activity.

Reconsolidation is believed to be a core neurobiological mechanism for the up-dating long-term memory [11-16], and available data indicate that relevant processes are at least partially distinct from those involved in the original consolidation of a memory [36]. Re-consolidation is also distinct from the process of memory extinction which forms the basis for several PTSD treatment strategies including exposure therapy [17, 37].

Neurobiological data strongly suggest that intrusive re-experiencing of symptoms in PTSD is partly a reflection of perturbed mnemonic processing involving hippocampal and amygdala networks, with the dysfunctional system possibly becoming a recursive intensification loop of triggered traumatic memories, such that the trauma memory dominates conscious and/or unconscious processes in the form of flashbacks and/or nightmares [38-40]. It appears that, once the critical trauma memory is re-consolidated into a non-threatening emotional form that no longer causes sympathetic activation, the recursive loop is broken and no longer able to dominate thought processes.

Through use of the LORETA algorithm, it was shown that post-RTM normalization in the scalp recorded EEG high-beta profile mostly reflects normalization of previously aberrant signals from the left hippocampus and amygdala, a finding fully consistent with above described neurobiological framework suggesting that the RTM protocol impacts memory re-consolidation processes mediated by the hippocampus and amygdala.

At present, the full relationship between EEG and behavioral observations requires further elucidation, especially because there were 3 subjects (each without elevated high-beta at baseline) who showed clinical improvements in the absence of EEG changes, and 1 subject who was clinically responsive with an increase in high-beta activity. Nevertheless, the data suggest that excessive high-beta activity may be a valuable biomarker of PTSD that can be used to provide neurobiological tracking of treatment efficacy. In considering this, it is important to note that approximately 50% of PTSD subjects in this study were on one or more psychoactive medications, most commonly SSRIs and/or anxiolytics. Brain EEG profiles are sensitive to many of these medications, and benzodiazepines are well established to cause increased beta activity. However, the large prior study by Begic and colleagues [32] which also showed increased beta activity in PTSD, enrolled only subjects that had been medication free for at least one month prior to evaluation. Also, none of our subjects changed their medications between baseline and the follow-up sessions which showed dramatically reduced beta levels.

The present study has several limitations, most notably the relatively small sample size and non-blinded design. Subjects were aware of their treatment status, as were clinical evaluators. However, EEG analyses were conducted in a blinded and automated manner. Longer term follow-up of patients will be desirable for future studies.

Whereas RTM appears to be exceptionally effective for eliminating re-experiencing and intrusive symptoms for treated events, and for leading to a reduction in associated aberrant avoidance and arousal behaviors, it does not fully protect against the impact of new traumatic events, which may trigger a return to

aberrant behavior patterns, as was seen for one subject in the overall study cohort . Combination of RTM (to deal with past events) and inoculation training (to increase resilience to future events) may therefore prove valuable.

Conclusions:

Consistent with prior work indicating PTSD-related structural and functional alterations in hippocampus, amygdala, frontal lobes, insula, and parietal lobes, excessive high-beta activity was seen originating from these (and other) structures, as measured by EEG. From a treatment perspective, this admittedly open-label study provides additional evidence on the clinical efficacy of the brief RTM protocol, with associated improvements in EEG profiles in a pattern which suggests that RTM does indeed achieve its effect through reconsolidation circuitry involving hippocampal, amygdala, and frontal regions.

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Supplementary Material 1: Perceptual modifications for the black and white movie		
Specific Association-dissociation manipulations		
Distance (increasing)	Move screen farther away- (from a few yards to as far back as two football fields, or farther as needed)	
	Variant	Vary distance of the self in booth from the self seated in theatre
Size	Shrink move screen so that the images/persons in movie get smaller	
Brightness/contrast	Vary brightness (white out detail--or provide sufficient light to see detail)	
	Variant	Decrease brightness (darken and obscure detail)
	Variant	Fuzz out distinctions (Decrease contrast / sharpness)
Angel/God Position:	Have the self in the projection booth float up above the theater watching the self in the booth (top of head and shoulders) watch Self in theatre (top of head and shoulders) as the self-in-the-theater watches the movie.	
Intermittent intervals	Watch every third (3^{rd}) second all-the-way through then watch every second(2^{nd}) second all-the-way-through, then watch every first (1^{st}) second	
Point of Focus	Focus upon different parts of the movie	Top half only
	Variant	Watch bottom half only[1]
	Variant	First watch top half all-of-the-way-through, then watch the bottom half all-of-the-way-through
Aspect ratio	Screen made taller and narrower or wider and shorter.	
Screen to Picture Ratio	White screen in background with small black and white movie in middle (Like a matted picture)	
Sequencing/simultaneous	Andreas (July 2016) Pick a point in middle of movie, run it rapidly from the middle of it to both ends--beginning and end--simultaneously. Instruction: "Imagine all events are like dominoes, so when you tip over the dominos at the worst moment of the movie, they will trigger the dominos on both sides so they	

	go from middle to both ends at the same time."	
Angles	The screen turns, or the client in theater moves so that self in theatre is watching movie at an oblique angle.	
Angled Booth	With the observing self in the projection booth, move the booth higher, to the left or to the right corner of the theater and view the side of Avatar's face/body in theatre	
Angle of movie	Imagine that the movie was taken from the side of the actors—a perpendicular third position.	
Speed/tempo of movie	Increase or decrease.	
Tilted screen	Screen/movie tipped forwards or backwards (tipping forward may invoke looming and should only be used with caution)	
	Variant	Screen/movie tipped sideways at skewed angle
Auditory Sub-modality distinctions (speakers next to screen)		
Tempo, Pitch, (Timbre) combo		
	Variant	Quick, high pitch, staccato (sounds like cartoon mice devouring cheese)
	Variant	Moderate tempo, Moderate pitch (sounds like Mae West--if voice or white noise--if sound)
	Variant	Slow, low pitch, elongated/stretched.
Olfactory Sub-modality Distinctions		
Adding smell in theatre when client fixates on movie smell	Popcorn smell added, smell of client's favorite movie food item added, etc.	
Notes: [1] Viewing the bottom half only may be dangerous for victims of sexual assault.		