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Short Communication

Regional Cerebral Blood Flow Changes Associated With Focal Electrically Administered Seizure Therapy (FEAST)

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ABSTRACT

Introduction: Use of electroconvulsive therapy (ECT) is limited by cognitive disturbance. Focal electrically-administered seizure therapy (FEAST) is designed to initiate focal seizures in the prefrontal cortex. To date, no studies have documented the effects of FEAST on regional cerebral blood flow (rCBF).
Methods: A 72 year old depressed man underwent three single photon emission computed tomography (SPECT) scans to capture the onset and resolution of seizures triggered with right unilateral FEAST. We used Bioimage Suite for within-subject statistical analyses of perfusion differences ictally and post-ictally compared with the baseline scan.
Results: Early ictal increases in regional cerebral blood flow (rCBF) were limited to the right prefrontal cortex. Post-ictally, perfusion was reduced in bilateral frontal and occipital cortices and increased in left motor and precuneus cortex.
Conclusion: FEAST appears to triggers focal onsets of seizure activity in the right prefrontal cortex with subsequent generalization. Future studies are needed on a larger sample.

Introduction

Electroconvulsive therapy (ECT) is the most effective intervention for the acute treatment of major depression, but significant cognitive disturbances have limited its use [1]. It is hypothesized that the cognitive side effects are due to the non-focal nature of the applied stimulus, triggering the onset of seizures in the medial temporal lobes and other areas outside the prefrontal cortex. Focal electrically administered seizure therapy (FEAST) was designed to deliver a spatially more focalized current as a way to restrict the onset of the seizure to the prefrontal cortex [2–4]. We used single photon emission computed tomography (SPECT) [5] to image the ictal onset and post-ictal termination phase of the seizure in a patient being treated with FEAST for major depression.

Methods

The subject, MSLR, was a 72 year old man with a 26 year history of major depression. He was recruited from the Medical University of South Carolina (MUSC) outpatient services where he presented for evaluation and ECT was found to be clinically indicated. He underwent a total of 12 sessions of FEAST therapy after signing an informed consent approved by the Institutional Review Board at MUSC. He also underwent a detailed assessment of his clinical presentation prior and during therapy. SPECT imaging was performed on three separate occasions: at baseline before treatments began, at ictal onset in his second treatment session and immediately after seizure resolution in his 4th treatment session.

At baseline, he scored 29 on the Hamilton Rating Scale for Depression (HSRD), 47 on the Inventory of Depressive Symptoms and 26 on the Suicide Scale Inventory (SSI). By the end of the 12 sessions he had an HSRD score of 5, IDS of 11 and SSI of 7. His IDS score was 43 when SPECT imaging was done (sessions 2 and 3). The patient exhibited no symptoms of post-ictal delirium and was fully

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oriented within 7 min in his second treatment session and within 30 s in his fourth treatment session. Measures of cognitive change included the mini-mental state examination (MMSE) on which MS scored 28 at baseline and 30 at the end of ECT sessions, AMI-SF etc.

FEAST

FEAST was administered with a modified MECTA spECTrum 5000Q device (MECTA Corporation, Tualatin, Oregon). Electrodes were attached in a standard manner to the MECTA remote-treat stimulus cables that were pre-identified as anode and cathode. The smaller electrode (labeled anode, 1.25 inch diameter) was placed anteriorly, with the lower boundary just above the center of the right eyebrow. The posterior electrode ($2 \times 3''$, oblong curved to match skull contour) was placed tangential to the midline and extended across the right supplementary motor cortex. FEAST administration lasted for 8 s. Seizures were effectively induced with a current of 800 mA and a charge of 230.4 mC. Other treatment parameters: pulse width 0.3 ms; frequency 60 Hz, and duration 8 s.

SPECT acquisition

Whole-brain SPECT images were acquired within 1 h of intravenously injecting 30 mCi (1110 Mbq) of technetium-99 bicisate (ECD; Neurolite, DuPont Pharma) and using a triple-headed Picker camera with low-energy ultra-high resolution fan beam collimators. All 3 SPECT imaging sessions were within a period of 10 days of each other.

SPECT baseline

The radiotracer was injected following a 15-min rest period during which the subject sat in a dark, quiet room with his eyes closed. Following the tracer injection, the subject rested for an additional 15 min before scan acquisition.

Ictal SPECT

With knowledge of the technetium-99 bicisate brain deposition time [6], the tracer was injected 12 s before the ECT electrical stimulus was applied. The seizure was monitored with EEG and lasted 225 s. The time required for full orientation following the end of the seizure was 4.7 min. Twenty minutes later the patient was escorted to the main hospital to have his mage acquired.

Post-ictal SPECT

The tracer was injected immediately following EEG seizure termination, which lasted 113 s, ended on EEG monitoring. The patient was fully oriented within 1 min of opening his eyes. Twenty minutes later the patient was escorted to the main hospital to have his image acquired.

SPECT image analyses

Images were processed on an Odyssey VP computer, using a low-pass filter with the default order of 2×0.32 as the cutoff. Images were attenuation-corrected and reconstructed transversely, then transferred to a Dell server for analysis. Preprocessing steps involved reorientation and brain extraction with FSL (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/). Each image was then co-registered with the MNI SPECT template using the non-linear registration tool of the BioImage Suite (http://bioimagesuite.yale.edu/index.aspx). The SPECT tool in the Bioimage Suite was developed specifically for within-subject comparison of seizure activity at various time points [7]. We performed statistical comparisons of ictal and post-ictal rCBF with the baseline scan.

Results

Early ictal activity was associated with significant increases (compared to baseline) in rCBF in the right superior frontal gyrus ($P = 0.001$), inferior frontal gyrus and insula ($P < 0.001$) (Fig. 1, Table 1).

Post-ictal comparison with baseline showed increased activity in the right lingual and precentral gyri ($P < 0.001$, $P = 0.007$ respectively). Significant hypoperfusion was observed in bilateral prefrontal and occipital cortices ($P < 0.001$).

Discussion

To our knowledge, this is the first human imaging study paired with FEAST. The findings support a pattern of localized seizure induction with FEAST in the right prefrontal cortex. Our results showed an increase in brain activity limited to the prefrontal cortex in the ictal scan with no significant increases in the temporal, parietal cortices, the cerebellum, the midbrain, the brainstem or subcortical structures such as the thalamus and the basal ganglia, as seen with ECT [8–10].

The therapeutic mechanisms of ECT are still a subject of controversy with several mechanisms thought to be involved including the regulation of cortico-limbic circuits, neurogenesis [11], and modulation of neurotransmitter release [12]. The PFC, along with subcortical limbic areas, appears to play the most prominent role. Post-ictal changes immediately after ECT show decreases in rCBF in the prefrontal cortex and limbic areas that were correlated with response to treatment [13] while changes days to months after

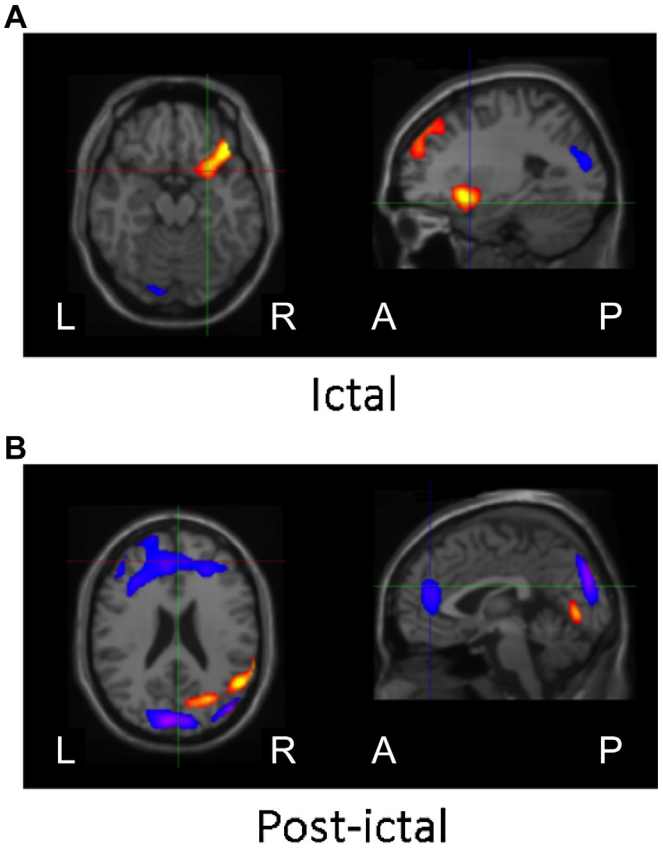

Figure 1. A) Ictal scan: statistically significant hyperperfusion (in yellow) was restricted to the right inferior and superior frontal gyri. B) Post-ictal scan: spread of hypoperfusion (in blue) taking over in the prefrontal cortex, with hyperperfusion in the motor and precuneus cortex. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 1
Areas of statistical significance in the ictal and post-ictal SPECT scans.

Condition	Brain region	*x*	*y*	*z*	*P*-value
Early ictal activity					
Hyperperfusion	Right superior frontal gyrus	14	44	25	0.001
	Right Inferior frontal gyrus	48	30	−12	0.001
	Right insula	30	20	−10	0.001
Hypoperfusion	Bilateral precuneus	1	74	38	<0.001
Post-ictal activity					
Hyperperfusion	Right precentral gyrus	26	−16	60	0.007
	Right lingual gyrus	14	−76	2	<0.001
Hypoperfusion	Right prefrontal cortex	−6	40	14	<0.001
	Left prefrontal cortex	4	44	14	<0.001
	Right occipital cortex	2	−88	14	<0.001
	Left occipital cortex	−14	−76	54	<0.001

treatment show increases [14–16]. fMRI data suggest that a reduction in functional connectivity in the PFC is an important therapeutic mechanism [17].

There is presumed specificity in the neural circuits that mediate the therapeutic benefit of ECT… rCBF, rCMR, and EEG slow wave changes in temporal areas have been linked to the magnitude of anterograde (AA) and retrograde amnesia (RA) [18,19]. Conversely, a theory proposed to explain the poor efficacy of low dose RUL ECT offers the notion that this modality triggers seizures principally from motor cortex, while at higher dosage RUL ECT also initiates seizures in PFC [18,20]. This perspective emphasizes sites of seizure initiation as more important in modulating efficacy than patterns of seizure propagation, since efficacy is hypothesized to be a function of the spatial distribution and strength of the inhibitory processes that terminate the seizure. As with secondarily generalized, focal seizures in epilepsy, surround inhibition is greatest at the site(s) of seizure initiation rather than in the secondary sites of propagation [19]. In essence, this theory suggests that evoking a robust inhibitory process in PFC regions is key to the antidepressant effects of ECT.

We have previously reported on the feasibility of right unilateral FEAST in a depressed population [3]. And while the efficacy found (35% remission) is inferior to classic BL ECT, the FEAST technology is still being optimized with electrode sizes and titration parameters. It is important to note that similar to the subject reported here, the cohort in general suffered no noticeable cognitive disturbance with FEAST. This is supported with the lack of involvement in the medial temporal lobes on SPECT early ictal imaging. More importantly, this case report suggests that the current unidirectional current applied with FEAST is certainly capable of initiating a focal seizure in the right frontal lobe before propagation.

Magnetic seizure therapy (MST) is also being considered as an alternative to classic ECT due to its better side effect profile. There have been no comparative trials between FEAST and MST but both appear to have a similar cognitive side effects [3,21]. MST is also thought to act by triggering more focal seizures [22] and regulating corticolimbic connections [23], but the underlying neural mechanisms have not been fully investigated. A critical issue in the ictal SPECT scanning method reported here is the timing of the tracer's injection. While some reports have suggested that 20 s are enough to have 80% of the technetium-99 bicisate deposited in brain, others have suggested a longer duration of 40 s. Our approach to start the injection 12 s before delivering an 8 s train of stimulation, with a longer duration for the technetium-99 bicisate to deposit in the brain, would conservatively lead to a less specific capture of the seizure onset. Yet despite of this variability in tracer pharmacodynamics, the results we present are even more suggestive of a focal induction in the right prefrontal cortex, near the site of the FEAST anode electrode placement. The generalization seen in the post-ictal scan, are also consistent with our expectations.

In summary, FEAST appears to induce a focal-onset seizure in the right prefrontal cortex prior to its generalization. It is also associated with an expected hypoperfusion in the post-ictal phase. Future work needs on a larger sample for more conclusive results.

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