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Review article

Autonomic biofeedback therapy in epilepsy

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ABSTRACT

Pharmacological intervention is a mainstay for treatment of epilepsy. However, a third of patients with epilepsy remain drug resistant. Behavioural treatments such as biofeedback training can be potential effective alternative interventions for drug resistant epilepsy. This paper describes a biofeedback therapy in which the training of patients to control peripheral autonomic tone (galvanic skin response) changes in central control of seizure occurrence. This paper introduces; 1) the theoretical development of methodology, 2) the effect of GSR biofeedback in reducing seizure frequency in drug resistant epilepsy, 3) insights into the neural mechanisms of effective GSR biofeedback through neuromodulatory autonomic control and 3) future prospects of this approach as a therapeutic tool instantiated as an Autonomic Cognitive Rehabituation Training (ACRT).

1. Introduction and rationale for development

Biofeedback is a procedure to enable the voluntary modulation of physiological responses through the provision of explicit (visual or auditory) feedback of covert physiological signals. Galvanic skin response (GSR), electrodermal activity (EDA) or skin conductance are indices of peripheral sympathetic nervous activity, reflecting sweat gland function. Unlike typically noradrenergic sympathetic post-ganglionic neurons, the effector synapse at the sweat gland is cholinergic and unaffected by circulating monoamines. GSR is a sensitive neural measure of emotional arousal and attention.

GSR biofeedback therapy for the management of epilepsy was established following a series of neuroscientific studies that identified an inverse relationship between electroencephalographic (EEG) indices of cortical neural excitability (slow cortical potentials) and peripheral sympathetic arousal (indexed by GSR activity) (Nagai et al., 2004b). Slow cortical potentials are direct current (DC) shifts within the EEG which often precede epileptic seizures (Birbaumer et al., 1990; Casper and Speckman, 1972; Speckmann and Walden, 1993). An increase in sympathetic activity reduces cortical excitation. The specific GSR biofeedback therapy for epilepsy is termed *Autonomic Cognitive Rehabituation Training* (ACRT) and consists of 12 consecutive sessions of 30 min of biofeedback training provided three times a week (Fig. 1).

2. Mechanisms of action

We demonstrated an inverse relationship between peripheral sympathetic activity (measured with GSR) and cortical excitability (with slow cortical potential: SCP) (Nagai et al., 2004b). The theoretical rationale behind this novel approach was the fact that negative cortical potentials reflect cortical arousal, which in turn is related to abnormal cortical excitability in epilepsy. GSR biofeedback training led to a reduction of cortical potential amplitude both in healthy participants (Nagai et al., 2004b) and patients with epilepsy (Nagai et al., 2009). One putative mechanism for the decrease in cortical excitability associated with increased sympathetic activity is via the modulation of thalamo-cortical sensory information flow. Correspondingly, in healthy subjects, our combined functional MRI (fMRI) and EEG investigation demonstrated that activity in bilateral thalamus, mid-cingulate and supplementary motor area (SMA) underlie SCP generation (Nagai et al., 2004c). Moreover, modulation of tonic sympathetic activity using GSR biofeedback specifically alters activity within the ventromedial prefrontal cortex / orbitofrontal cortex ((VMPFC/OFC) (Nagai et al., 2004d)). Here, activity is negatively correlated with skin conductance level. This region is a component of the default mode of network, wherein the activity increases during states of relaxation and decreases when attention is externally engaged. Patients with epilepsy show functional impairments of this network, which may underpin alterations in consciousness (Gotman et al., 2005; Blumenfeld, 2011; Caciagli et al., 2014). Better volitional control of neural activity within the VMPFC/OFC, acquired through biofeedback training, is thus likely to contribute to enhanced management of seizure occurrence in patients with epilepsy through an impact on information traffic across distributed brain regions.

3. Results

In a first randomized controlled trial (RCT) involving 18 patients

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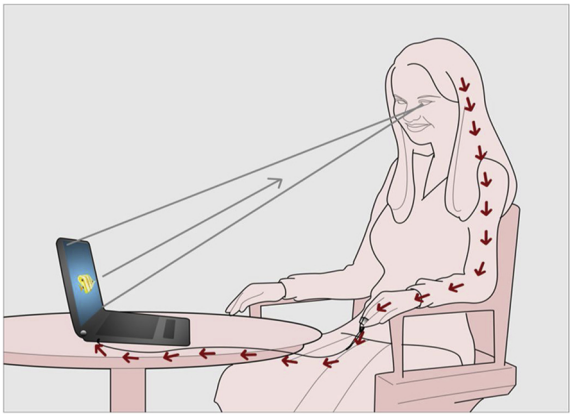

Fig. 1. GSR biofeedback example (Nagai et al., 2018: EBioMedicine).
An animation moves forward with increase in skin conductance and backward with decrease in skin conductance. The sequence of animation represents a pictures of a fish, a mermaid, a famale person, an angel and a star when the patient's sympathetic tone increases.

with drug resistant epilepsy, we demonstrated that seizure frequency was significantly reduced in the active biofeedback group after one month of therapy training, compared to the sham control group ($p = 0.001$) (Nagai et al., 2004a). Within the biofeedback group, seizure frequency reduced significantly ($p = 0.017$) with an average percentage seizure reduction of 49% (SD = +/- 41.64, median 56.4%) and a response rate of 60%.

We since conducted a wider clinical trial involving 40 patients with drug resistant temporal lobe epilepsy (TLE). We also used neuroimaging to investigate neural mechanisms supporting seizure reduction. We tested the prediction that intrinsic resting state network connectivity, particularly between DMN and limbic networks, predicted improvement in seizure frequency in this patient group.

All patients in the therapy group successfully modulated GSR level in the desired direction. There was a significant between-group difference in percentage seizure reduction ($p < 0.001$: Mann-Witney U Test). The therapy group had a significant reduction in seizure frequency after one month of intervention ($p < 0.001$: Wilcoxon Signed Rank Test) with a mean seizure reduction of 43.0% (SD = ± 32.12, median = 37.26). The response rate was 45%, representing 9 out of 20 patients demonstrated more than 50% seizure reduction. One patient became seizure-free. On the other hand, there was an increase in seizure frequency in the control group (treatment as usual) by 31.1% (SD = ± 88.27, median = 0) (Fig. 2).

Neuroimaging analysis revealed that post-therapy seizure reduction was linearly correlated with enhanced functional connectivity between amygdala and the orbitofrontal cortex (OFC). This implicates the uncinate fasiculus as a key pathway in generation and suppression of seizures in patients with TLE (Fig. 3).

4. Tolerability and safety

ACRT was well tolerated by the patients with epilepsy. The approach of ACRT therapy is behavioral, and to date no significant side effects have been reported in research and clinical therapeutic settings over the last 20 years. However, a systematic prospective investigation is required in a forthcoming larger clinical trial.

5. Planned studies

A double blinded RCT is currently planned, which will extend the accessibility of proven psycho-physiological intervention for adult patients with drug-resistant epilepsy. This trial will utilize a digital

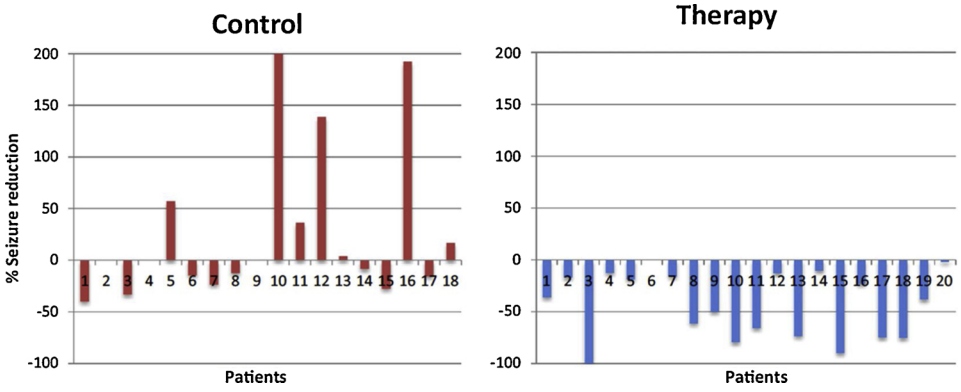

Fig. 2. Seizure freuency changes after a month of therapy (Nagai et al., 2018: EBioMedicine).
% Seizure frequency changes after GSR biofeedback therapy in control and biofeedback groups. Percentage seizure frequency change = [(Post averaged seizure frequency-baseline averaged seizure frequency)/ baseline averaged seizure frequency] x 100. The averaged seizure frequency change of Control group = 31.10% (SD = ± 88.27, median = 0), Therapy group = 43.0% (SD = ± 32.12, median = 37.26).

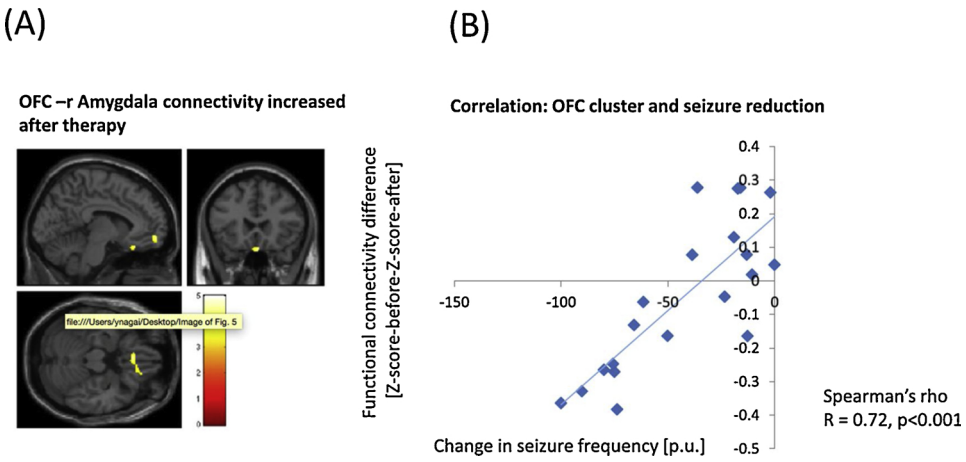

Fig. 3. Functional connectivity changes after a month of therapy (Nagai et al., 2018: EBioMedicine).
A) Two distinctive functional connectivity changes to Right Amygdala was observed in Orbitofrontal Cortex (OFC) and Frontal Pole (FP). B) The identified OFC area is linked to the regulatory center of skin conductance which was previously discovered. The amygdala-OFC connection linearly correlated with degree of seizure reduction. All results are significant a $p < 0.05$, after FWE correction at cluster level.

version of ACRT therapy, which patients with drug resistant epilepsy will be able to access from home and follow guidance on the software platform. This approach will enable us to perform a study approaching the sample size of a pharmaceutical clinical trial.

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