Why Neurofeedback and Biofeedback are Effective Means to Assess and Impact Behavior

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What is EEG Neurofeedback?

Thorndike (1911) in light of Pavlov's classical conditioning studies proposed the existence of operant conditioning via the concept of the "law of Effect" to explain why responses emitted in a satisfying circumstance occur more frequently and responses occur less frequently in a discomforting situation. B.F. Skinner who extensively studied operant conditioning argued that instrumental or operant learning involves rewards that are reinforcers of stimulus-response (S-R) links that do not require mental processes such as intention, representation of a goal, or consciousness (Skinner, 1953). Skinner defined the rules of operant conditioning by showing that the consequences of a reward or punishment increases or decreases the probability of the response where the reward or punishment was called a "reinforcer". The reinforcer is an effective reward or punishment delivered after a response that increases or decreases the future probability of that response occurring again. The reinforcer once associated with a reward or punishment can also be the feedback signal that predicts a future reinforcer, for example, if a spontaneously emitted behavior results in the delivery of a stimulus, e.g., a click or tone, which predicts receiving a reward or punishment in the future, then the feedback signal itself will increase or decrease the probability of the behavior occurring in the future. The terms positive and negative in operant conditioning also apply to the presentation or removal of reinforcement.

This definition of operant learning was first applied to human brain activity by Knott and Henry (1941) involving blocking of the EEG alpha rhythm. In 1962, Joe Kamiya (1971; 2011) elaborated on the study by Knott and Henry by demonstrated voluntary control of the alpha rhythm. Fox and Rudell in 1968 extended operant conditioning to single units and multiple units via implanted electrodes in cats. They demonstrated that operant conditioning is possible at the level of single neurons when they reinforced changes in the firing patterns of single neurons located in the motor cortex of cats (Fox and Rudell, 1968; O'Brian and Fox, 1969). Wyrwicka & Sterman, (1968) also demonstrated operant conditioning of the EEG sensory motor rhythm (SMR) in cats. These studies were followed by a series of animal and human operant conditioning studies involving groups of neurons, local field potentials, evoked potentials and EEG (Rosenfeld et al, 1969; Rosenfeld & Fox; 1971; Fox et al, 1970; Fox & Rudell, 1970). The use of operant conditioning to affect epileptic discharge and sleep spindles in cats was reported by Sterman et al (1970a; 1970b) and Sterman and Friar (1972). Since 1971 there have been over 690 peer reviewed human EEG biofeedback journal articles listed in the National Library of Medicine database. The goal of these studies was to reduce symptoms and improve clinical outcome in patients with a wide variety of disorders, for example, attention deficits, obsessive compulsion, anxiety, epilepsy, traumatic brain injury, schizophrenia, depression, hyperactivity, autism, aspergers to name a few. Patients undergoing EEG biofeedback do not willfully or intentionally change their own brain waves but rather simply attend to a signal, discrete or continuous stimulus, that is linked to a future reward and therefore is called a "reinforcer". The future reward is something of value to the subject, for example, doing better in school, reduced

symptoms and complaints or tangible items like a toy, or candy, or a lollipop or money, etc. that the subject achieves if they meet the criteria for EEG change determined by the clinician. Real-time functional MRI (fMRI) biofeedback is a new but expensive method to modify specific brain regions, however, it only requires one or a few sessions because of specificity and money is often given to subjects as a future reward (deCharms, 2007; Caria et al, 2011). It is beyond the scope of this book to review the details of the wide number of protocols or types of feedback signals or scalp locations or EEG features that were the target for modification using operant conditioning. There are several excellent reviews of this literature (Thompson and Thompson, 2003; Demos, 2004; Budzinsky et al, 2008; Evans and Abarbanel, 1998; Robbins, 2008). It is important to note that EEG biofeedback is not limited to the sensory motor rhythm (SMR) nor to the post reinforcement synchronization process that follows the delivery of reward in some circumstances, instead, operant conditioning of single neurons and groups of neurons throughout the brain has been published (Fox and Rudell, 1968; Rudell and Fox, 1972; Fox et al, 1970) as well as in invertebrate animals that do not exhibit SMR (Nargeot et al, 1991; 1999b; 1999c; 2001; 2009; 2011).

QEEG and Neurofeedback

The 'Q' in QEEG means quantification. Non-QEEG is defined as 'eye-ball' visual examination of the EEG traces without the use of quantification or spectral analyses of the EEG traces. All EEG biofeedback methods that date from the early 1960s used computers to spectrally analyze the EEG, therefore, EEG biofeedback is also a QEEG method. I will not use the 'Q' because it is understood that all EEG biofeedback relies upon quantification by a computer. EEG biofeedback also called Neurofeedback is not an active task and instead involves a subconscious learning procedure called 'operant conditioning' where a given EEG event, e.g., increase in alpha rhythms (8 - 12 Hz) above some threshold value results in the delivery of a signal or reinforcer to the patient and there is no intent, no muscle activity or cognitive decisions or even consciousness awareness. As a consequence of the simple pairing of a reward signal with the occurrence of the brain event then the probability of the reinforced brain event increases over trials. The critical factors are: 1- Specificity by targeting the 'weak' or dysregulated hub or module linked to a patient's symptoms also called 'contingency', 2- temporal contiguity between the onset of the subconscious EEG event and the delivery of the feedback signal and, 3- the magnitude of a future reward as indicated by the feedback signal. The 1st systematic and well designed EEG biofeedback studies were conducted in animals in the 1960s (Fox and Rudell, 1968) including studies of reduce incidence of epilepsy in cats by Sterman et al (1971). The 1st human EEG biofeedback study was published by Knott and Henry in 1941 with operant conditioning of alpha blocking. The first systematic and well designed human EEG biofeedback study was by Joseph Kamia in 1972 (Kamia, 1972). Since this time the National Library of Medicine database includes 1,490 citations when using the search terms 'EEG biofeedback' and there are 5,258 citations using the search terms 'Brain Computer Interface' which almost all involve EEG biofeedback to control devices of various sorts, especially robotic arms in quadriplegics and other types of paralysis.

The animal studies involved the use of operant conditioning to modify single neurons and groups of neurons (O'Brian and Fox, 1969) and evoked potentials and EEG (Fetz, 1969; Fox and Rudell, 1968; 1970; Rosenfeld and Fox, 1971; Fox et al, 1970). More recent animal studies to

operantly condition single neurons and groups of neurons has confirmed and extended the early animal work (Sakurai et al, 2014; Kobayashi et al, 2010; Fetz, 2013; Ishikawa et al, 2014).

There is no doubt that one can use operant conditioning also called instrumental learning to modify brain waves just like the brain wave event is an overt behavior as long as one follows the standard operant conditioning principles. Thorndyke in1911 and B.F. Skinner in the 1940s-1960s explored in great detail the critical factors involved in operant conditioning (Skinner, 1953). The critical factors are that there must be a significant reward or potential for a future reward before operant conditioning will work. Also, there needs to be reasonable temporal contiguity between the brain event and the delivery of a signal that predicts a future reward. The key is the ability of neural systems to link the contingency of the reinforcer or reward signal to the probability of a future reward. If the contingency networks and synapses are modified via dopamine and other neuromodulators by the temporal linkage of the brain event and the feedback signal then the firing patterns of neurons will be modified and successful operant conditioning of the EEG will occur. If the methods are flawed, e.g., not measuring real brain activity and only artifact or poor or delayed temporal contiguity or not a sufficient reward value then it is unlikely that real operant conditioning of neurons or neural circuits will occur.

Neurophysiological Mechanisms of Neurofeedback

Ballein and Dickinson (1998) and Schultz (2006) summarize the modern neuroscience of instrumental learning or operant conditioning in the mammalian brain. The Ballein and Dickinson (1998) model integrates all of the essential and well established factors involved in instrumental learning and it is important to read the details of their theory. Here I will rely upon the instrumental learning theory of Ballein and Dickinson (1998) and adapt the Schultz (2006) equation to Z score biofeedback. Dopamine is a fundamental neuromodulator involved in reward prediction and instrumental learning and it is manufactured primarily in the ventral tegmental area (VTA) and the areas the VTA innervates such as the nucleus accumbens (NAc), amygdala, hippocampus and prefrontal cortex (PFC) (Fields, 2008; Schultz, 1998; Schultz et a, 1997; Mirenowicz and Schultz, 1994). The physiological basis for EEG biofeedback was demonstrated in studies by Schultz et al (1997) and Schultz (1998) who showed that dopamine neurons of the VTA are activated by the presentation of unexpected rewards and inhibited by omissions of expected rewards. These and other similar studies support a model of learning based on diverg3ences from expectations. As discussed by Schultz (2006) and Birbaumer et al (2009) there are four factors involved in operant conditioning: 1- contiguity, 2- contingency, 3- predictive error and, 4- specificity. Contiguity concerns the requirement of approximate simultaneity between the "emitted" or spontaneous neural event and a reinforcer or feedback signal that predicts a future reward. The window of time during which contiguity operates and neural memory traces are present is referred to as the "Contiguity Window". Contingency refers to the requirement that a reward needs to occur more frequently in the presence of a brain event as compared to its absence in order to induce long-term potentiation in excitatory neural loop systems (Ballein and Dickinson, 1998). Ballein and Dickinson (1998) systematically varied reward contingency by varying the value of the reward including devaluation and showed that reward is encoded in the associative neural structures controlling performance. Prediction error

was first noticed by Kamin's (1969) blocking effect which demonstrated that a fully predicted reward does not contribute to learning, even when it occurs in a contiguous and contingent manner. These studies showed that neural network modifications underlying operant conditioning advances only to the extent that there is uncertainty that the feedback signal or reinforcer predicts a future reward. Network modification progressively slows as uncertainty of the reinforcer decreases. The repeated temporal contiguity between the emitted neural event and a signal results in a neurophysiological association if the signal predicts a future reward. As a consequence of the pairing of the signal with the neural event then the probability of the emitted EEG event occurring in the future increases as a function of the association and this is represented by a curve of reduced prediction error over trials also called a learning curve (Schultz, 2006). Specificity was discussed in the History section where it is explained that the goal of specificity is good clinical outcome with fewer sessions.

Operant conditioning is also referred to as instrumental S-R bonding and dopamine and the pre-frontal cortex are critical in forming an association or linking a neural event or "state" to a signal predicting a future reward at the synaptic level of brain function as described by Kandel (2006) and many others. Iteration in excitatory neural loops results in long-term potentiation (LTP) and growth of synapses (Buzsaki, 2006). The EEG is the summation of synaptic potentials and therefore changes in the frequency, coherence and phase between neurons is the result of synaptic changes which are based on the same basic molecular mechanisms of synapse modification described by Kandel (2006) that are operating in both invertebrate and vertebrate learning and memory. In addition to Dopamine, Acetylcholine (ACH) and serotonin are also critical for the acquisition of new memories. Similar to Dopamine, ACH's role is to facilitate the activity of NMDA receptors that control the strength of connections between nerve cells in the brain. ACH facilitates NMDA receptors and enhances synaptic long-term potentiation (LTP) necessary for learning and memory formation (Buchanan et al, 2010). Dopaminergic neurons located in the dorsal lateral and dorsal medial striatum as well as the medial frontal lobes and anterior cingulate gyrus mediate different aspects of reward-related learning with the dorsal medial striatum being especially important in operant conditioning (Bromberg-Martin, 2010; Corbit and Janak, 2010). Bernacchia et al (2011) showed that dopamineric neurons located in the cingulate gyrus, parietal lobes and prefrontal cortex exhibit different time constants of memory traces from milliseconds to seconds and are important in all instrumental learning. It was argued that different time intervals exist between different events and the occurrence of a signal that predicts a future reward and accordingly there are neurons with different memory trace time constants that link a signal to a future reward (Bernacchia et al, 2011). Bromberg-Martin & Hikosaka (2009; 2010) trained two monkeys to move their eyes (saccade) towards either of two targets on a screen to receive a small or large water reward. The targets did not predict the size of the reward; rather, saccading to one of the targets triggered a cue that provided information about the size of the upcoming reward, whereas saccading to the other target triggered a non-informative cue. Single-neuron recordings revealed that midbrain dopamine neurons increased their firing in response to an informative cue indicating a large upcoming reward and were inhibited by a cue indicating a small reward. In trials with uninformative cues, the neurons responded only to the reward itself. Importantly, the neurons were also more excited by the target that indicated an informative cue would appear on the screen than by the target indicating an uninformative cue. Furthermore, Cohen et al (2012) found persistent activity of GABA neurons in the ventral tegmental area (VTA) during the delay between a reward-predictive cute and the reward that reflected the value of the upcoming reward (big, small or

none). These studies suggest that GABA neurons encode reward expectation and thus are not affected by the reward itself. Thus, midbrain dopamine neurons signal not only the expectation of a future reward but also the expectation of information about the reward.

It is important to note that some promote the myth that the only form of biofeedback is reinforcement of a particular rhythm in the brain called the sensory motor rhythm (SMR) which is present in the motor cortex in humans and animals and that a post reinforcement synchronization (PRS) is essential for EEG biofeedack (Sherlin et al, 2012). This is clearly a myth because operant conditioning has been demonstrated for many different frequencies in many different regions of the brain including single neurons, multiple units, evoked potentials and EEG independent of SMR or PRS (Fox and Rudell, 1968; 1970; Fox et al, 1970; Fetz, 1969; Kobayashi et al, 2010; Sakuri et al, 2014). Also, invertebrates such as Aplysia do not exhibit SMR nor post reinforcement synchronization (Nargeot et al, 1999a; 1999b; 1999c; 2009).

A formal model that includes all aspects of instrumental learning (i.e., operant conditioning) incorporates the neuroscience of neuromodulators where the strength of operant conditioning C is dependent on the magnitude of a future reward R (e.g., candy, lollipops, toys, money), the delivery of a distinct and clear feedback signal F and the temporal contiguity or delay between a neuromodulator "memory trace" or T' and the specific/contingent neural event(s) S that preceded the onset of the feedback signal F, like a click or light flash, DVD, videos, etc. The equation is $C = (S \times F \times R)/T'$. If S is repeatedly time locked to the expectation of a future reward of magnitude R then operant conditioning C occurs. If F is weak or not discernable as a signal of a future reward then C = 0. C is directly proportional to S, F and R and inversely proportional to the time between the specific neural event(s) S and the delivery of the feedback signal F. T' is a bounded interval because zero delay is within the masking interval for some events and in the case of fMRI neurofeedback delays of 20 seconds have been reported. The apostrophe in T' represents a bounded time interval from about 250 msec to several seconds. The larger the magnitude of a future reward than the greater the amount of dopamine (& other neuromodulators) and therefore the more synaptic change but the longer the interval of time between the event and the feedback signal then the lower is C. The operant S is a neural event, like a behavior but at the micro or network level and represented by brief moments of stable relations between neurons where the probability of the occurrence of S is reinforced by the presentation of the feedback signal (F) that predicts a future reward (R). T' is represented by standard integrate-fire neurons with multiple neuromodulator memory traces and loops where there is an overlap in time between S and the feedback signal within the contiguity window. The equation as shown below is $O = (S \times R)/T'$. Reenterant excitatory loops and LTP reinforced by dopamine and other neuromodulators results in modification of network connectivity as measured by the qEEG. The qEEG is the cortico-cortical, thalamo-cortical, cortico-thalamic and reticular cortical circuits discussed in the Introduction and neurofeedback is a modification of the circuitry through operant conditioning.

The synchrony of pre-frontal temporal contiguity at the neurophysiological level and thus the "memory trace" time constants are related to dopamine production in pre-frontal, parietal and cingulate cortical neurons (Balleine and Dickinson; 1998; Corbit and Janak, 2010; Bernacchia et al, 2011). EEG biofeedback as represented by changes in the frequency, coherence, phase, amplitude, etc. as a result of operant conditioning is based on the neurophysiological mechanisms present in all animals as enumerated by Balleine and Dickinson (1998); Schultz (2006).

Behavior is mediated by neurons where bursts of action potentials predate overt movement. For example, the readiness potential that occurs seconds prior to the awareness of the intent to act or when the motor cortex sends action potentials to brainstem and spinal cord neurons that then mediate a given action. Successful movement produced by bursts of action potentials also produce memory traces so that if a future reward is time locked to the action potentials then the synapses responsible for the successful behavior are reinforced and increase in size and number. Operant synaptic modification is not limited to overt behavior since single neurons and groups of neurons can also change firing patterns based on operant conditioning (O'Brien and Fox, 1969; Fox and Rudel, 1968; 1970; Fox et al, 1970; Rosenfeld et al, 1969, Rosenfeld and Hetzler, 1973; Sterman et al, 1970; Bawin et al, 1964). Since the 1960s there have been hundreds of publications demonstrating changes in the EEG as a function of reinforcement, including most recently, the related branch called "Brain-Computer-Interface" studies in paralyzed patients (Wilson et al, 2009; Brunner et al, 2011; Bauer and Gharabaghi, 2015).

Critics of EEG Neurofeedback

Recent critics of Neurofeedback use multi-million dollar double blind studies and fail to find a difference between the placebo and control group (xx). However, after careful scrutiny one finds incompetence and invalid methods that explain the failure and there is no need to dismiss the large and historical scientific foundations of operant conditioning based on these flawed studies. For example, Eric Kandel (2006) studied the basic neurophysiological processes involved in sensitization, habituation and both classical and operant conditioning (instrumental learning) and showed that these mechanisms are invariant across phylogeny from aplysia to humans for which he was awarded the Nobel prize in 2000. Robert Nargeot and colleaques further extended Kandel's studies of learning in aplysia by focusing extensively on the neural mechanisms of operant conditioning (Nargeot et al, 1991; 1999b; 1999c; 2001; 2009; 2011). Classical and operant conditioning are how we acquire a predictive understanding of the world. Operant conditioning/instrumental learning is where a spontaneously emitted behavior or neural activity is reinforced or punished thereby changing the probability of a future reoccurrence of the behavior or neural activity. Positive reinforcement such as by food or drink or pleasure increases the probability whereas negative reinforcement reduces the probability. The critical factors necessary for operant conditioning are: 1- specificity (contingency) where particular brain hubs and modules linked to symptoms are selected for modification, 2- contiguity where delivery of a signal of a future reinforcement/punishment near to the time of occurrence of the behavior and, 3- magnitude of the reward itself, e.g., food reinforcement in a satiated animal will not lead to operant learning. These principles of operant conditioning are the same for behavior or a burst of neural activity which predates behavior where a neural event produces a behavior at some baseline rate and if followed by a reinforcement or punishment then the probability of the occurrence of a future behavior or neural event changes.

The genetic and molecular mechanisms of synapse modification that has survived millions of years of animal evolution including each person reading this document represents a very stable and foundational process and it is not surprising that these mechanisms are also the foundation of human EEG biofeedback where neuron behavior is modified by reinforcement or punishment. The modern terminology of Brain-Computer-Interface (BCI) slowly emerged in the 1980s with the use of digital computers to detect a threshold and deliver a operant conditioning
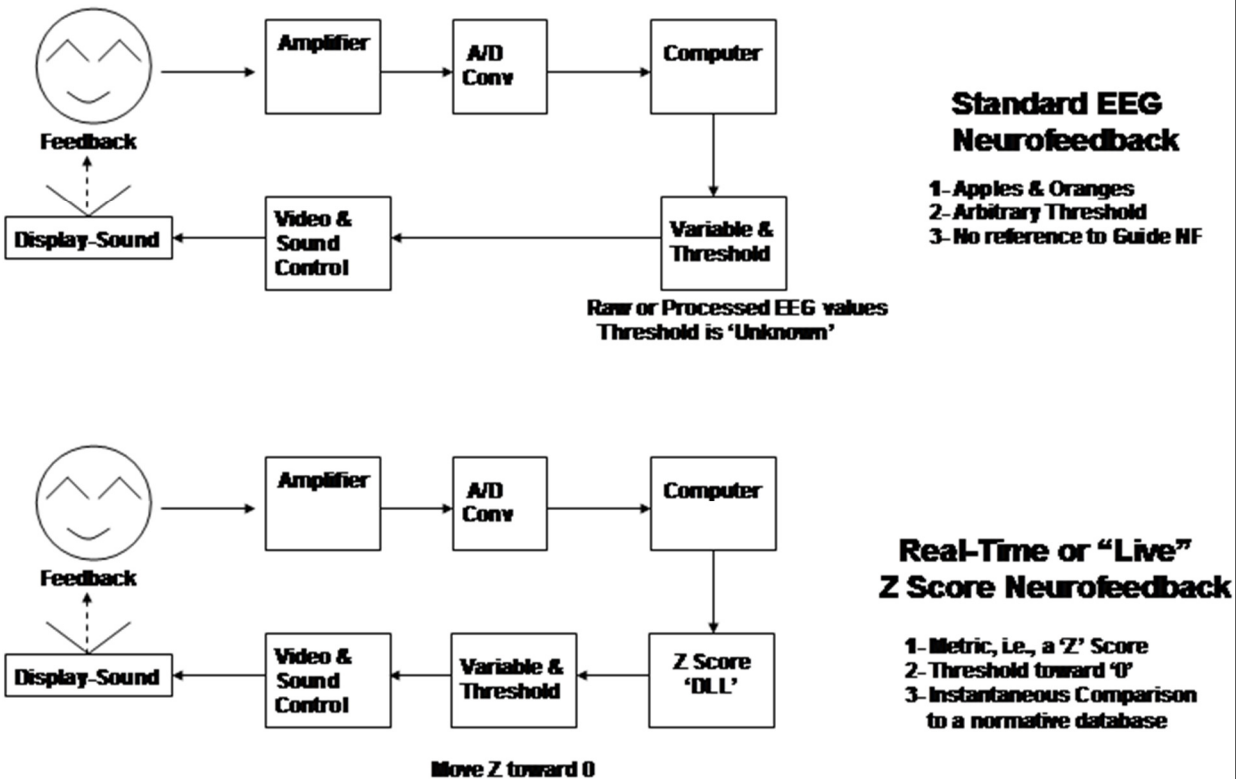
feedback signal (Wilkison, 1983). The use of an emitted neural event to control a computer cursor (i.e., the EEG mu rhythms 10 - 12 Hz in sensorimotor scalp regions) was published in 1991 by James Wolpaw and colleaques (Wolpaw et al, 1991). The goal was to use operant conditioning of the EEG to aid spinal cord damaged patients and other disabled patients to control computer controlled objects. Wolpaw et al (1991) were the first to use the term Brain-Computer-Interface (BCI) and to use the EEG to control a computer cursor. Since 1991 over 5,000 BCI studies are cited in the National Library of Medicine database. However, both EEG biofeedback also called Neurofeedback (NF) and BCI involve operant conditioning of neural synapses to modify the EEG. NF also involves the use of computers to detect EEG features but differs in the main goal of controlling an external device in the case of BCI instead of the more general goal of modifying particular EEG frequencies in particular locations. The emphasis on control of external devices in physically disabled patients (BCI) vs changing the EEG in patients with psychiatric/psychological disorders (NF) is less important than the common aspects of EEG operant conditioning that is shared by both NF and BCI.

Z Score Neurofeedback used by NeuroCore, Inc.

In the 1990s a new form of EEG biofeedback was suggested in which real-time comparisons to an age matched reference population of healthy or normal subjects are used as a guide or "compass" to increase specificity and provide a uniform direction and threshold for the biofeedback process (Thatcher, 1998b; 1999; 2000a; 2000b). Prior to Z score biofeedback clinicians had to guess about what threshold to set for a given frequency or location to trigger the feedback signal or reinforcer signal. The clinician had to ask and answer questions like: Shall I reward alpha rhythms when they exceed 10 uV? or 20 uV?, shall I inhibit theta rhythms when they exceed 5 uV or 10 uV? What threshold for coherence shall I use for a particular age or scalp location?   What EEG frequency and amplitude will be the threshold for a given scalp location or age? Over the years different protocols were developed where "one size fits all" were adopted independent of age or symptoms. There was a lack of standardization and an abundance of arbitrary threshold selections prior to the advent of Z score biofeedback which was first implemented in 2006 by Brainmaster, Inc. and Thought Technology, LLC and Deymed, Inc., EEG Spectrum, Neurofield, Inc. and Mind Media, Inc. became rapidly accepted with over 3,500 users in the year 2016.

Z score biofeedback greatly simplifies and standardizes EEG biofeedback by reducing many different metrics that are like apples and oranges (absolute power, relative power, ratios, coherence, phase) to a single or common metric of the Z score or a standard deviation with respect to the EEG from a group of age matched healthy normal subjects. Z score biofeedback also takes the arbitrariness and guess work out of setting a threshold to determine the when to deliver a reward signal. For example, there is a unifying objective of reinforcing EEG measures of all kinds toward $Z = 0$ which is the center of the age matched normal population. This is like providing real-time feedback of a blood test for cholesterol or liver enzymes and reinforcing movement toward the standards of a normal healthy population.   The figure below illustrates the difference between conventional EEG biofeedback vs. Z score biofeedback.

Difference Between Standard Neurofeedback vs Z Score Neurofeedback

Standard EEG Neurofeedback

1- Apples & Oranges
2- Arbitrary Threshold
3- No reference to Guide NF

Raw or Processed EEG values
Threshold is 'Unknown'

Real-Time or "Live" Z Score Neurofeedback

1- Metric, i.e., a 'Z' Score
2- Threshold toward '0'
3- Instantaneous Comparison to a normative database

Move Z toward 0

Top row is conventional or standard EEG biofeedback in which different units of measurement are used in an EEG analysis (e.g., uV for amplitude, theta/beta ratios, relative power 0 to 100%, coherence 0 to 1, phase in degrees or radians, etc) and the clinician must "guess" at a threshold for a particular electrode location and frequency and age to when to reinforce or inhibit a give measure. The bottom row is Z score biofeedback in which different metrics are represented by a single and common metric, i.e., the metric of a Z score and the guess work is removed because all measures are reinforced to move Z scores toward Z = 0 which is the approximate center of an average healthy brain state based on a reference age matched normative database in real-time.

The introduction of EEG normative databases in 1994 dramatically changed the face and direction of EEG biofeedback by providing a objective measure of pre vs post treatment and aiding in the identification of dysregulation in brain regions linked to symptoms (Thatcher, 1998). Real-time Z score neurofeedback introduced in 2006 further changed the face of EEG biofeedback by providing an instantaneous feedback as to the direction and magnitude of reinforcement of increased stability and efficiency in brain networks. The introduction of a series of symptom check lists of networks based on the neuroimaging scientific literature paved the way for 3-dimensional Brodmann area and network NFB in 2010 that further increased specificity and linkage of patient's symptoms to the patient's brain.

Different normative databases can be constructed and validated by using basic scientific standards of gaussianity, cross-validation, amplifier matching and peer reviewed publications (John et al, 1987; Thatcher and Lubar, 2008). A recent example of a new application of a normative database is the use of complex demodulation as a Z score Joint-Time-Frequency-Analysis (JTFA) for the purposes of real-time biofeedback (Thatcher, 1998b; 1999; 2000a; 2000b; Thatcher et al, 2003; 2005a). The Z score is computed in microseconds limited by the sample rate of the EEG amplifier and therefore are "instantaneous" Z scores. The process does not occur at the speed of light and does require slightly less than 1 microsecond, however, this speed of computation is for all practical purposes "instantaneous". It is necessary under the principals of operant conditioning that contiguity not be too fast because the activation of dopamine is relatively slow and long lasting. Therefore, 250 mec to 1 sec are commonly used intervals between the detection of a brain event meeting threshold and the delivery of a reinforcement or the contiguity interval which are common in standard EEG biofeedback that does not involve Z scores.

In 2006 the real-time Z score biofeedback method was implemented by Brainmaster, Inc. and Thought Technology, LLC., and later by Mind Media, Inc., Deymed, Inc. Neurofield, Inc. and EEG Spectrum, Inc. as well as Applied Neuroscience, Inc. All implementations of "Live Z Score" biofeedback also referred to as real-time Z score biofeedback share the goal of using standard operant learning methods to modify synapses in brain networks, specifically networks modified by long term potentiation (LTP) and NMDA receptors. Operant conditioning is known to involve changes in the same NMDA receptors that are modified in LTP and therefore the unifying purpose of Z score biofeedback is to reinforce $Z = 0$ of the EEG which is the statistical "center" or set-point of a group of healthy normal subjects. The normal subjects are a reference just like with blood tests for cholesterol or liver enzymes showing deviation from normal. The concern that reinforcing toward $Z = 0$ would move individuals in the direction of "mediocrity" or "average" intelligence and function.   However, this assumption has not been observed over that last decade in numerous publications (see the partial list of publications below).   The reason that the reinforcement of instantaneous Z scores toward $Z = 0$ is clinically effective is because 'chaotic" regimes and extremes of dysregulation are reflected by moments of extreme instantaneous Z scores. Reinforcement of "stable" and efficient instances of time results in increased average stability and efficiency in dysregulated nodes and connections in networks linked to symptoms (see chapter 1.2.9). An analogy is a disruptive child in school classroom where the teacher gives an "M & M" to the child when the child is quiet and not disruptive. Over tine the child will be quiet and more cooperative due to the reinforcement. Z score biofeedback is also consistent with models of "homeostatic plasticity" in which the learning rule of local inhibitory feedback is increased stability and regulability by oscillation around $Z = 0$ (Hellyer et al, 2015).

Appendix A includes a partial list of Z score neurofeedback studies.

rtfMRI vs EEG Neurofeedback

Functional MRI (fMRI) is a measure of changes in blood flow produced by changes in the rate of neuron action potentials in large clusters of neurons. There are limitations in both the temporal and spatial accuracy of fMRI because there are significant delays between the time of increased action potential production and glial signals that result in dilation of arteries that

change blood flow over a wide area.   Positron Emission Tomography (PET) measures the arterial side of blood flow change while fMRI measures the de-oxygenation in veins due to oxygen utilization by neurons.   The veinus drain system collects de-oxygenated blood in ever increasing diameters as the blood flows back to the heart and lungs. The temporal delays in the detection of a change in de-oxygenation vary from about 10 seconds to over 100 seconds (Liao et al, 2015). Attempts at improving temporal resolution to less than 5 seconds have been attempted with poor results because of the low signal-to-noise ratios with short TR times in a magnetic (Hinds et al, 2011; Stoeckel et al, 2014).   The spatial decoupling between activation of clusters of neurons and changes in de-oxygenated blood is partly because of the drainage system but also because large areas of blood flow change occur even in areas where there is no change in neural activity (O'Herron et al (2016).   A common saying in fMRI circles is that blood is like watering a garden where if only roses need water the brain nonetheless waters the entire garden. Also, fMRI suffers from low cross-validation validity and high false positive rates especially for small spatial cluster analyses (up to 70% false positives over the last 15 years involving possibly 40,000 fMRI publications) (Eklund et al, 2016).

So-called "real time" functional magnetic resonance imaging (rtfMRI) is not actually real-time if many seconds are involved, nor is it highly spatially localized. In other words, the term "real-time" is a stretch because there is commonly a 10 to 20 second delay between the detection of a blood oxygen level dependent or BOLD signal. In comparison, EEG that is truly "real-time" because it operates in the sub-millisecond domain and with EEG Biofeedback it is common for there to be less than a 10 millisecond delay between the detection of a neural event and the delivery of a feedback signal. Nonetheless, rtfMRI allows for a non-invasive view of brain function and has the potential to be used in clinical treatment itself via rtfMRI neurofeedback.   rtfMRI neurofeedback similar to EEG biofeedback or EEG neurofeedback has been used to alter patterns of brain activity associated with cognition or behavior while an individual is inside the MRI scanner even with 10 to 20 second delays between the detection of a change in the brain and the delivery of a feedback signal (Birbaumer et al., 2006; 2009; deCharms, 2008; deCharms et al., 2004; 2005; Weiskopf et al., 2003; 2007).

Cost and Portability Comparisons Between rtfMRI and EEG Biofeedback
The therapeutic potential for rtfMRI is severely limited by both technical limitations such a poor temporal and spatial resolution but also due to the high cost, lack of portability and low reliability.   For example, a MRI scanner costs around three million dollars compared to less than $10,000 for an EEG amplifier and computer software capable to of providing Brodmann area level of EEG biofeedback.   Maintenance costs are high for a MRI scanner, for example, about $40,000 per month for liquid helium and a large support staff is needed. In comparison there are no monthly maintenance expenses with QEEG and a single technician can be trained to perform 3-dimensional Brodmann area level EEG neurofeedback. Also, a MRI magnet weighs about 11 tons while an EEG amplifier is portable and weighs less than 5 pounds and can be held in the palm of the hand.   Also, the bore of a MRI magnet causes claustrophobia and many subjects refuse to enter the bore of the magnetic and children are often sedated so that they hold still inside the magnet.   Today, dry and wireless EEG headsets allow subjects to move around without artifact and for hyperactive children and autistic children to be cooperative while awake and without discomfort.

The technical limitations cannot be glossed over like the advocates of rtfMRI do. For example, action potential bursting can be via groups of inhibitory neurons or excitatory neurons

but blood oxygenation changes in fMRI do not distinguish between inhibition and excitation. In contrast, EEG is produced by summated inhibitory and excitatory synaptic potentials that can be distinguished. rtfMRI has low spatial resolution on the order of many centimeters because dilation of arteries and oxygenation of the blood in veinus drainage paths is spatially vast and as explained the brain waters the entire garden when only a small part of the garden needs watering. In contrast, EEG inverse solutions have spatial resolutions of about 1 cm and temporal resolution of 1 msec (Grech et al, 2011; Pascual-Marqui, 1999). rtfMRI is severely limited in functional connectivity measurements because of the very low temporal resolution (10 seconds to 100 seconds) and low signal-to-noise ratios. As a consequence rtfMRI is limited to very low frequencies, e.g. 0.01 (Stoeckel et al, 2014). The facts are that the brain operates at quite high frequencies, e.g., > 100 Hz or 10 msec and there are high speed phase shifts and changes in coupling between ROIs and clusters of neurons in less 50 msec (Thatcher et al, 2009a). In contrast to rtfMRI functional connectivity using LORETA coherence and LORETA phase difference and LORETA phase reset provide millisecond temporal resolution and allow clinicians to reinforce changes in the magntiude and delays in coupling between nodes and hubs of networks linked to symptoms. Furthermore, rtfMRI has difficulty measuring "Effective Connectivity" or the magnitude and direction of information flow between Brodmann areas and Hubs of networks linked to symptoms. The reality is that LORETA EEG biofeedback has adequate spatial resolution and high temporal resolution that allows clinicians to target Brodmann areas and regions of interest (ROIs) to increase or decrease current density in these regions as well as the functional and effective connectivity between the regions. Finally, only raw scores and not Z scores are used in rtfMRI which means that a clinician must guess whether to reinforce or inhibit the BOLD signal in a brain region. What if neural activity is compensatory or within a normal range and the clinician guesses, at very high expense, to use rtfMRI to reinforce an area that is already excessive? The use of QEEG real-time Z scores or comparisons to an age matched healthy population increases clinical efficacy and helps minimize adverse reactions and reduces the number of sessions necessary to obtain increased stability and efficiency of information processing in brain networks.

Recently a biased review of rtfMRI was published (Thibault et al, 2016) that essentially dismissed the over 1,400 peer reviewed EEG Biofeedback publications cited in the National Library of Medicine database (Pubmed) and claimed that EEG Biofeedback failed to show differences in comparison to a sham control group. The study that was cited was a flawed study and unrepresentative of the vast majority of EEG Biofeedback publications. At the same time, the authors praised rtfMRI but failed to emphasize the severe limitations of rtfMRI described above. In addition, the authors of the biased review failed to cite a single LORETA EEG biofeedback study even though the science is nearly 20 years old. Another example of bias is a failure to cite the study by Keynan et al (2015) involving rt-fMRI and EEG with validation of changes in the electrical activity of the amygdala. Here is a URL of a You Tube Video demonstration of sLORETA Z score biofeedback that shows the simplicity, low expense and ease of use of qEEG as a EEG biofeedback method to target dysregulated brain network hubs and connections linked to the patient's symptoms:
https://www.youtube.com/watch?v=P76LgSIFcDQ

Appendix – B is a partial list of LORETA EEG biofeedback studies that Thibault et al (2015) failed to cite where each are superior to the vast majority of rtfMRI bofeedback studies.

## Relative Sensitivity and Validity of QEEG Neurofeedback vs rtfMRI Neurofeedback

From 2010-2011 the US Army at Fort Campbell tested 2 – 4 channel Z score Neurofeedback as part of the Warrior Resilience Rehabilitation program for soldiers from Afghanistan suffering from PTSD and/or mild traumatic brain injury. The results of the Neurofeedback treatment were of sufficient benefit to implement LORETA Z score neurofeedback in 2012. Currently, Fort Campbell has purchased six NeuroGuide Z score Neurofeedback systems that are now a part of the standard of care for injured soldiers. Below is a diagram that illustrates the Fort Campbell neurofeedback system.

Neuroimaging Neurofeedback - Fort Campbell
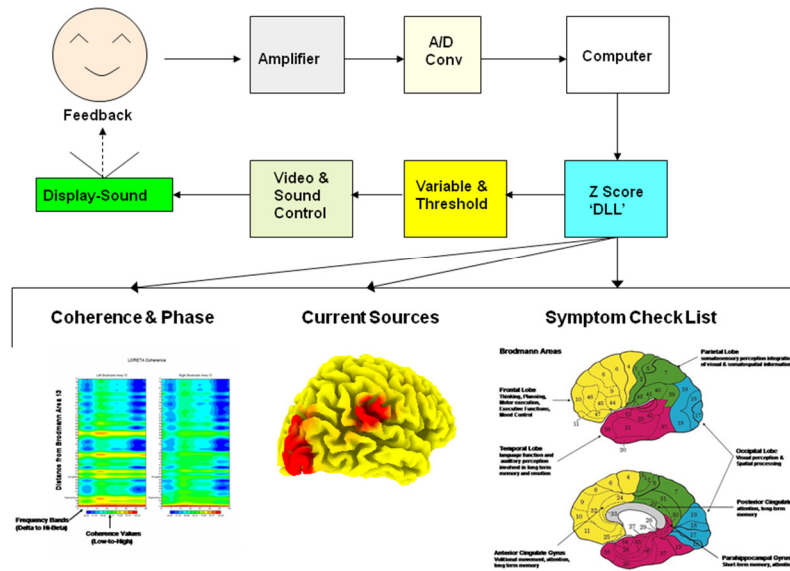
Below is an example of pre vs post treatment in a PTSD soldier after 10 sessions. More sessions

Examples of Electrical Neuroimaging After Neurofeedback
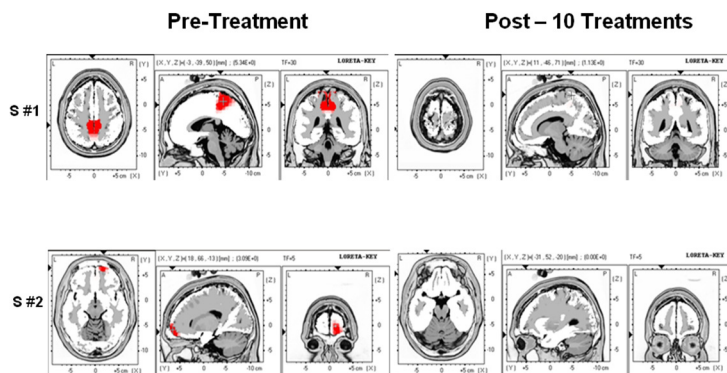
Below are figures from a randomized double-blind neurofeedback study that compared fMRI biofeedback of blood flow changes with LORETA EEG biofeedback of the attention network. Pre vs post fMRI demonstrated that the double-blind and placebo control study with only 20 minutes of Z score LORTA EEG biofeedback significantly altered blood flow in the attention network. This study has not been published as of the date of this writing, however, it was presented to a public audience at the University of Munich Medical school by Daniel Keeser. Ph.D. Title page to a double-blind and placebo-controlled comparison between a single 20 minute session of rtfMRI vs a single 20 minute session of LORETA Z score neurofeedback.

Below is a figure of the randomized double-blind Z score Neurofeedback study design
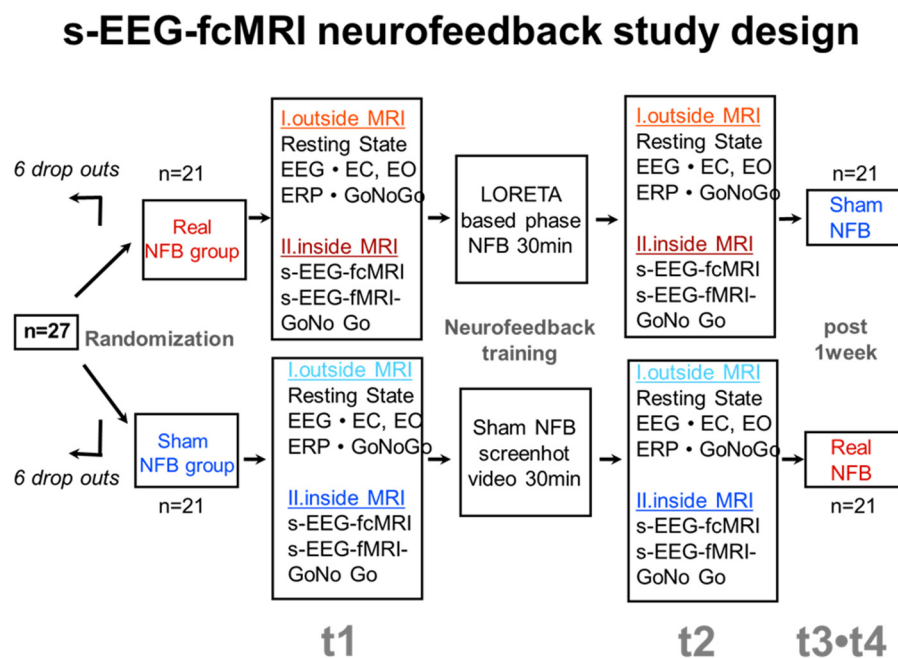
Below is a figure showing the results in which there was no change in the placebo control while both the rtfMRI and LORETA Z score neurofeedback altered blood flow in the attention network
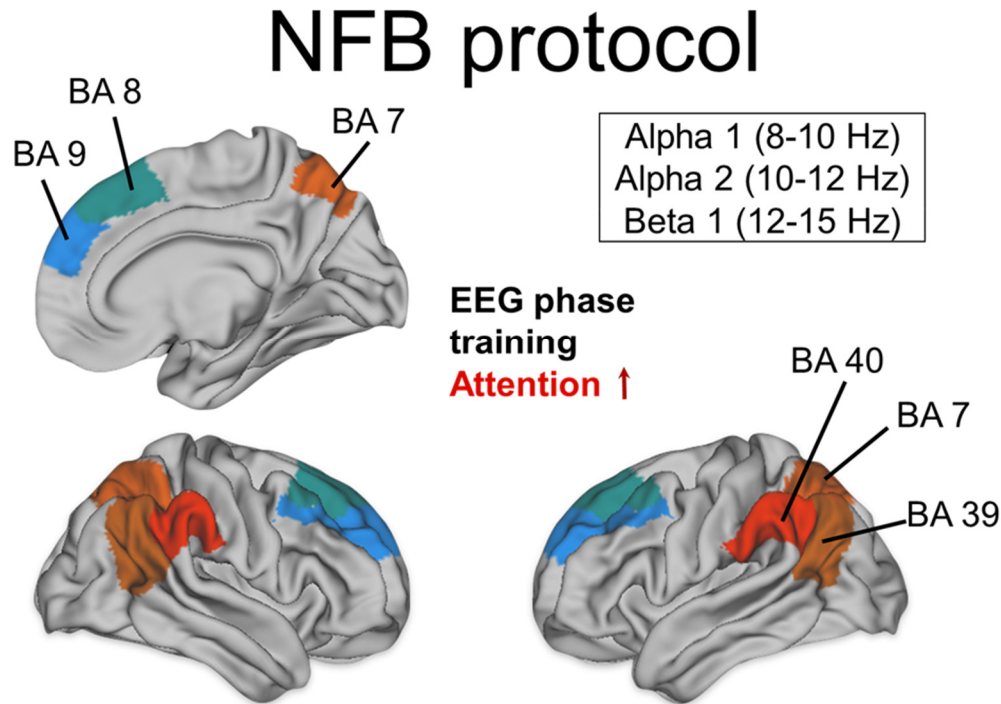
In summary, EEG Neurofeedback has a long and well established scientific history and scientific foundation. The National Library of Medicine (Pubmed) cites 1,493 peer reviewed publications in which the vast majority involved control group comparisons with significant effect sizes. The number of double blind studies was cited in a previous document and the vast majority of these studies also demonstrated significant effect sizes. As mentioned previously, a few recent double blind studies failed to find a significant difference between controls and experimental subjects. However, careful examination of the methods and procedures showed that flawed methodology was involved. As discussed in earlier sections operant conditioning will not occur if flawed methodology is used.

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APPENDIX – A

A Partial List of EEG Z Score Neurofeedback Publications

Collura, T.F. (2009) Practicing with Multichannel EEG, DC, and Slow Cortical Potentials, NeuroConnections, January. 35-39.

Collura, T., Guan, J., Tarrent, J., Bailey, J., & Starr, R. (2010). EEG biofeedback case studies using live z-score training and a normative database. Journal of Neurotherapy, 14(1), 22–46.

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Collura, T. (2008). Time EEG Z-score training: Realities and prospects. In: Evans, J., Arbanel, L. and Budsynsky, T. Quantitative EEG and Neurofeedback, Academic Press, San Diego, CA.

Keeser, D. Kirsch, V,Rauchmann, B, et al. The impact of source-localized EEG phase neurofeedback on brain activity-A double blind placebo controlled study using simultaneously EEG-fMRI- (submitted for publication-2017).

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Koberda JL (2015) Application of Z-score LORETA Neuro-feedback in Therapy of Epilepsy. Neurol Neurobiol Volume1.1: http://dx.doi.org/10.16966/noa.e001

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APPENDIX – B

Partial List of LORETA EEG Neurofeedback Publications

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