Briefing Paper

Applied EEG Neuroscience Innovation for Mental Health

Stuart Black, BSc(Eng) MSc CEng MIET

April 2021

Table of Contents

Executive Summary

This paper has been prepared to brief policy and decision makers. It summarises the challenges of existing interventions for mental health, the innovation potential of applied EEG neuroscience, and the barriers to achieving widespread benefits.

It does not cover the impact of Adverse Childhood Experiences (ACEs) or provide details of how Neurofeedback therapy is delivered. These topics are more fully covered in other papers[1].

Existing interventions for mental health have significant limitations. Medication effects are temporary, the mechanisms are poorly understood, and have significant side effects. Existing psychosocial interventions such as talking therapies are ineffective in many cases, and are difficult to scale.

The traditional model for mental health categorisation (DSM) is under challenge – in response there has been a surge in research into the electroencephalogram (EEG) and mental health.

The neuroscience of the EEG has the potential to transform mental health diagnosis through EEG brain mapping, and mental health treatment through EEG biofeedback therapy.

EEG biofeedback therapy aka neurofeedback therapy overcomes the limitations of psychiatric medication and talking therapies. There is a strong base of academic and clinical evidence.

Neurofeedback therapy is available privately now, and has been funded in isolated cases by two NHS Clinical Commissioning Groups and one Local Authority. It is scalable and delivers a return-on-investment of £80,000 - £117,000 per patient.

NICE's approach to this therapy has been protectionist, biased towards preserving the status quo. Evidence is routinely downgraded in quality without justification, a 'chicken & egg' dichotomy is perpetuated by resisting the approval of interventions not in wide clinical practice, and economic benefits are unjustifiably underplayed.

The return on investment and health economics assessment is compelling. The widespread application of this healthcare technology has the potential to make a significant impact on the £68bn pa cost UK cost of unremediated childhood trauma.

Limitations of current mental health interventions

Mental health provision is complicated by the predominance of two groups of professionals with divergent perspectives on the nature of mental health issues:

- The psychiatric view tends to view mental health disorders as imbalances in brain chemistry and favours treatment by prescribing medications;

- The psychological view treats mental health disorders as behavioural issues and favours remediation through talking therapies.

Medications can be very powerful and effective, yet they don't address the root cause and will only work as long as they are being taken. The mechanisms of many mental health medications are unclear, serious side effects are common, and most are not licenced for children. Methylphenidate, the active ingredient of Ritalin, commonly prescribed for ADHD, is a Class B controlled drug.

Psychosocial therapies that require the trauma to be reimagined (e.g. Talking therapies, EMDR) are ineffective for many traumatised children, adolescents and adults, for two main reasons:

- Their minds don't remember the trauma (though their bodies, including their nervous systems, do), so the therapy won't work;

- Their minds do remember the trauma and they find it too overwhelming to re-visit it, so the therapy can't work.

Of those that do engage in talking therapies, only 50% of patients show reliable improvement[2].

Notwithstanding their limited efficacy, psychosocial mental health interventions are difficult to scale. There were critical shortages of the professionals to deliver them before Coronavirus.

This challenge will become more pressing as we emerge from the pandemic, as early research indicates[3]. Previous research on extended lockdowns indicated that 30% of children displayed PTSD symptoms[4].

Future of Mental Health Diagnostic Criteria & EEG

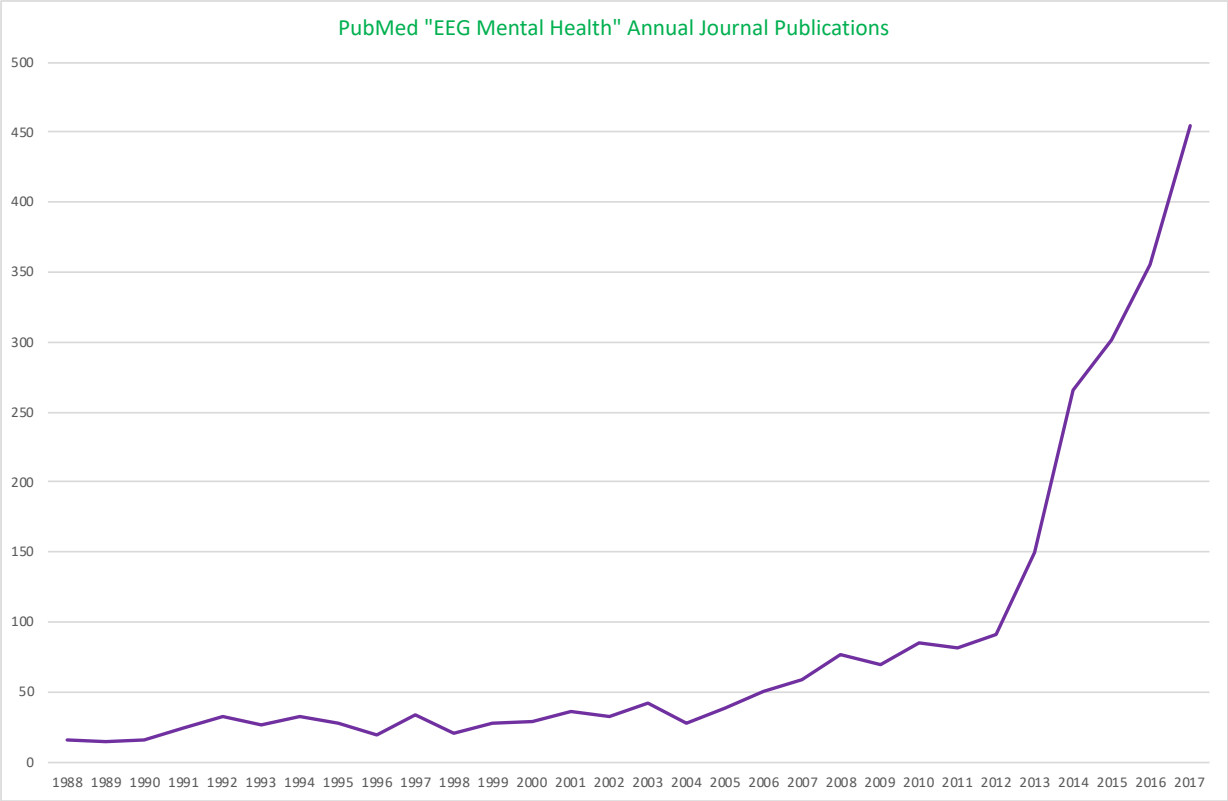
The "Diagnostic and Statistical Manual of Mental Disorders Fifth Edition" (DSM-5) is the "bible" of mental health disorders.

It has a controversial history. Up to DSM-3, homosexuality was described as a mental health disorder. A meeting in 1974 voted 61% to 39% to remove it. In 2013, DSM-5 decided that if you were still grieving for someone more than 12 months after their death, you may have "Bereavement Disorder".

The DSM's future is uncertain. In 2013, weeks before DSM-5 was issued, the US National Institute of Mental Health announced that it would be diverting research funds from the symptom-based "set of labels" of the DSM, to research that supports a new classification system, as "Patients with mental disorders deserve better."[5]

The rationale was that "Mapping the cognitive, circuit, and genetic aspects of mental disorders will yield new and better targets for treatment"[5].

One effect of this has been a surge in research into the science of the electroencephalogram (EEG), or “brainwave” signals generated by neuronal activity that can be measured with sensors on the scalp, and the relationship of the EEG to mental health:



Application of EEG Neuroscience to Mental Health

There are two main applications: Quantified EEG Analysis; and EEG Neurofeedback Therapy.

Quantified EEG Analysis

EEG analysis is an established medical technique for neurological investigations of suspected epilepsy conditions, for monitoring brain activity in Intensive Care Units (ICU) or during surgery, and supporting investigations into dementia and stroke[6].

Quantified EEG analysis also known as ‘brain mapping’ techniques have been available since the advent of personal computers.

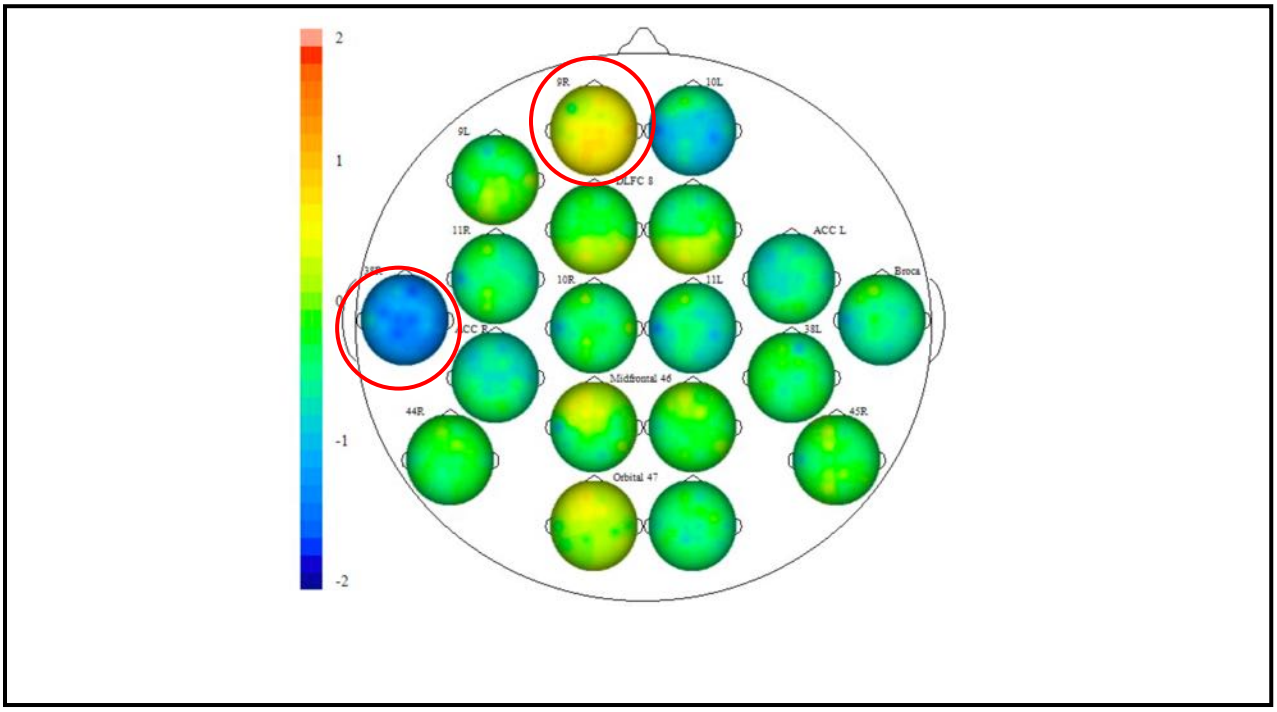
Until recently these techniques have been focused on comparing a subject’s EEG patterns with those of a ‘normative’ database. The scientific validity of the concept of characterising an ‘average’ brain in this way is questionable[7, 8]. We term these ‘Standard QEEG Brain Mapping’. They provide a lot of data (numbers) but lack information, analysis and insight.

More recently, techniques have evolved to identify patterns or markers within the EEG that correlate with specific traits.

In 2013 NEBA® Health[9] obtained FDA approval[10] of a device to assist with ADHD diagnosis by measuring the ratio of theta:beta brainwaves*.

Juri Kropotov[11,12,13] in St Petersburg and David A Kaiser[14],[15] in Los Angeles have led the research efforts to establish these 'neuromarkers' for a range of traits and histories.

Neuromarkers** have been identified for multiple traits through external and empirical research, including the analysis of 'Death Row' inmates EEG patterns. This has evolved into what we term an 'Advanced QEEG Brain Mapping' capability, akin to a mental health x-ray:



**Example Neuromarkers – a participant in Surrey County Council Virtual School Project showed markers for Attachment issues and Anxiety (highlighted in red)

We use these brain maps to inform, educate and empower clients. To explain how their brains have adapted in response to life events (neuroplasticity), that this is entirely normal, but that this can leave them with unhelpful response habits once the event has passed.

Also that thanks to neuroplasticity, whilst their past explains how they are now, that doesn't have to define their future.

There are several unexplored applications for EEG analysis:-

- Screening for the impact of acquired brain injury before symptoms emerge, enabling preventative measures to be put in place. Military and sports injuries are examples.
    - For example, to screen trauma survivors for markers that indicate susceptibility to mental health disorders.

* EEG activity frequency bands are named after Greek letters: Delta = 1-4Hz, Theta = 4-7Hz, Alpha = 8-15Hz, Beta = 16-31Hz, Gamma = 32-40Hz. A sub-type of ADHD has been correlated with a high ratio of Theta to Beta activity.

    - We also identified an opportunity to predict the onset of tinnitus in the military, and made proposals to the Centre for Defence Enterprise. Correspondence with the Medical Director Defence Medical Services on our proposals for tinnitus research is in Appendix D.
- Parole “before” and “after” assessments of EEG neuromarkers to assess changes in prisoners psychological profile.
- Asylum seekers psychological profiling, i.e. Do they indicate problematic traits?

Biofeedback and EEG Biofeedback, aka Neurofeedback Therapy

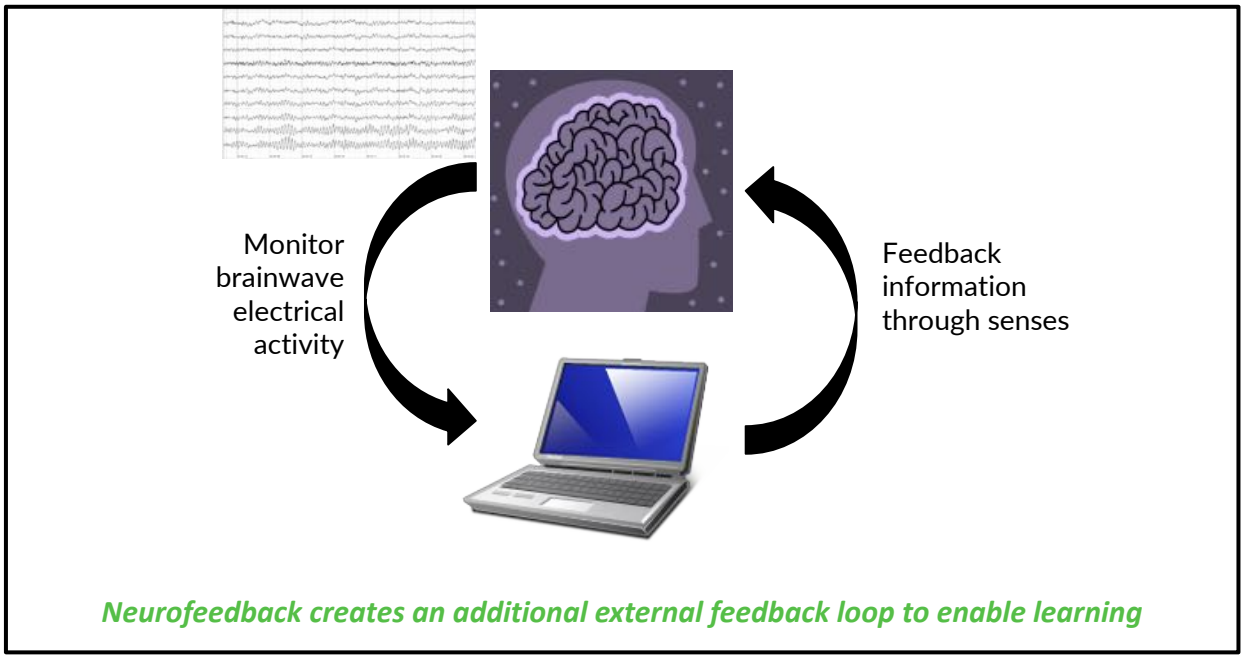
Biological feedback is essential to life, and hundreds of individual feedback systems have been identified within our bodies[16], operating to regulate our internal physiology according to the established mechanisms governing those systems.

For example, in healthy individuals blood sugar levels are regulated by releasing insulin from the pancreas when blood sugar levels rise, and stopping the release of insulin when the desired level is reached.

Some aspects of our physiology we are aware of, for example our breathing or our heart-rate. But there are other aspects of our physiology including our brain’s electrical activity (EEG) that we cannot observe, hear, feel, smell or taste.

Bio-feedback training creates additional external feedback loops between our physiology and the control system for that physiology (the brain and nervous system), facilitating learning, either consciously or unconsciously, to alter our physiological regulatory mechanisms[17].

EEG-Biofeedback, also known as Neurofeedback therapy or Neurotherapy, is a form of bio-feedback to improve brain regulation and function. An external feedback loop is created to take information from the brain’s electrical rhythms, process it and feed it back to the brain via the senses:



Neurofeedback creates an additional external feedback loop to enable learning

This method has an estimated 10,000 practitioners in the USA[18], with clinical application to mental health disorders including anxiety, depression, attention and hyperactivity[19], neurological disorders including migraine, epilepsy, traumatic brain injury, and studies on peak performance applications[20].

Evidence Base and Development of Approach

Neurofeedback therapy for trauma has a strong evidence base from research and clinical practice.

The evidence goes back to 1989 when Dr Eugene Peniston treated alcohol-abusing Vietnam Veterans. Of 30 subjects, only 2 relapsed over a 13-month period[21].

Later studies found efficacy to address PTSD symptoms in the same population (Vietnam Veterans), for example a 1991 Peniston randomised controlled trial had a relapse rate of 100% within the control group vs. 20% in the Neurofeedback group[22].

A 2005 randomised controlled trial[23] of 120 substance-abusing inpatients at the CRI-Help residential treatment program in Los Angeles, with double-blinded outcome measures, showed that the experimental group achieved an abstinence rate of 77% compared to 44% for the controls, at 12 months.

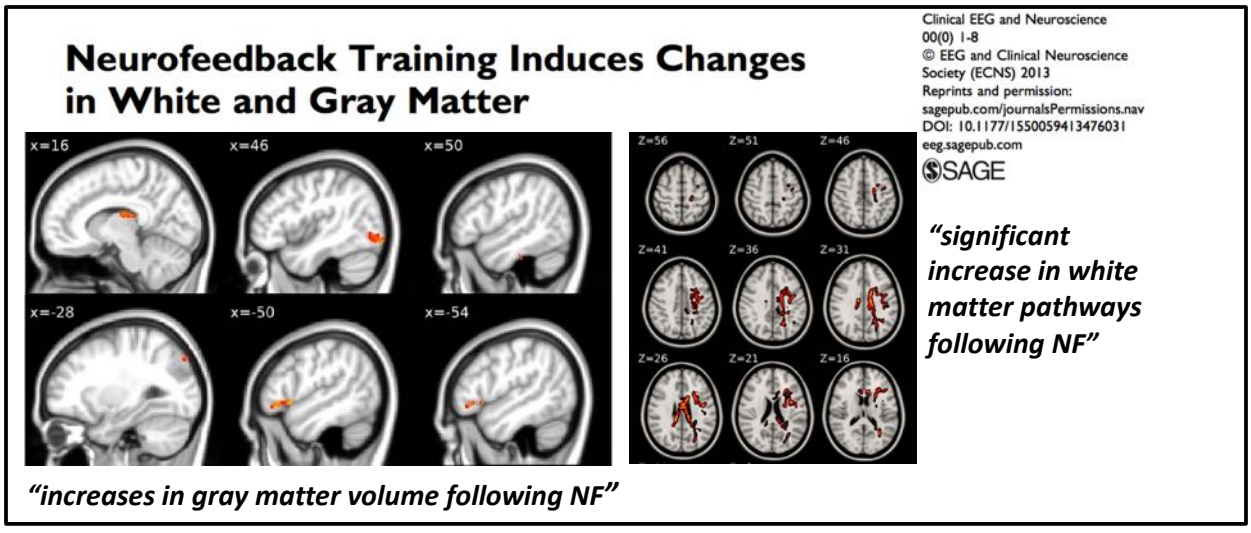
In 2016 a randomised controlled trial was published concluding that neurofeedback therapy produced significant symptom improvement in individuals with chronic PTSD[24].

Although there is always a desire for more studies, larger studies and more blinded studies[25], the placebo question was answered a long time ago. Neurofeedback therapy was discovered serendipitously by Barry Sterman through possibly the ultimate placebo-controlled, fully-blinded experiment.

This is described in detail in <u>Appendix B.</u>

Since Sterman's discovery, the field of Neurofeedback therapy has evolved.

Studies have demonstrated the physiological effects of neurofeedback, in terms of increasing grey-matter volume and white-matter tracts pathways[26]:



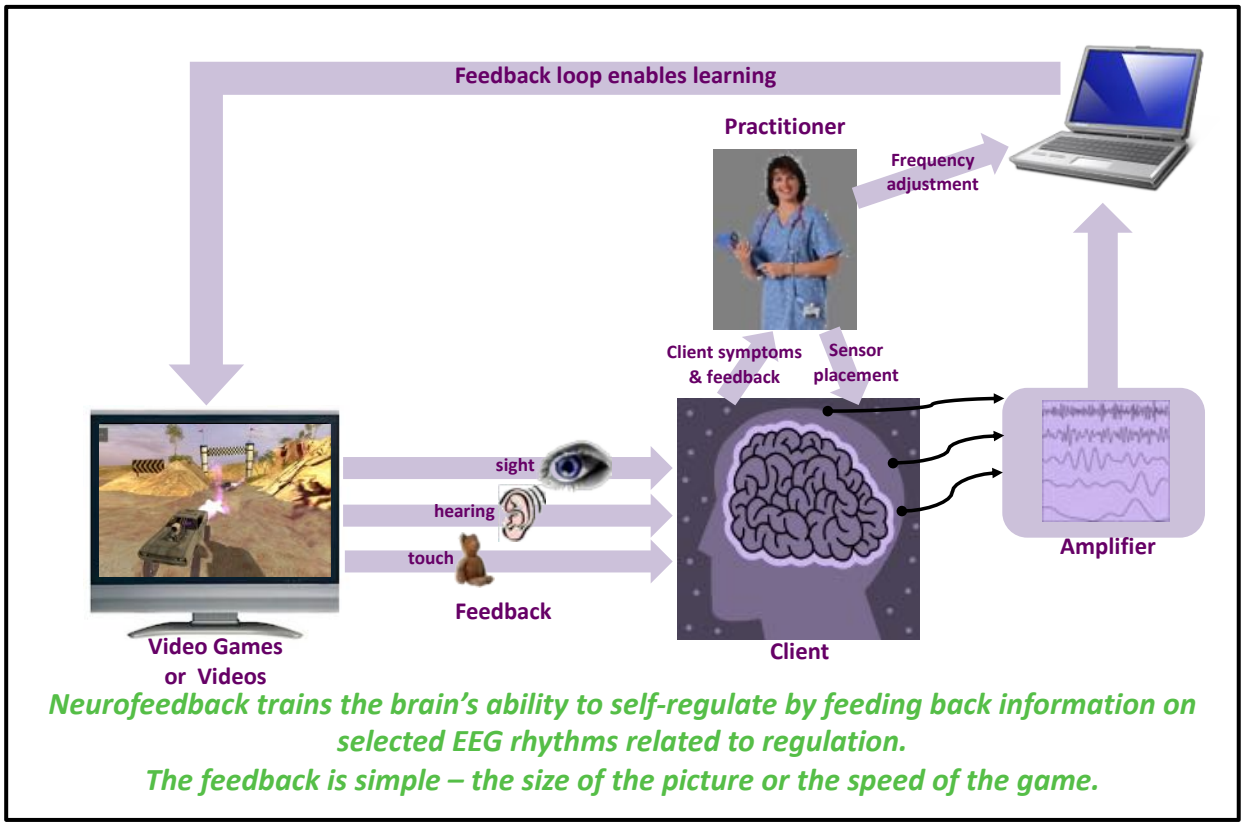
The field has developed from the beginnings where 'one size fits all' directive approaches were the standard, where all subjects presented the same way and all those in the experimental group were subject to the same experimental design.

Contemporary methods are tailored to the individual, representing personalised or precision medicine[27].

Non-directive methods have emerged that target hubs of the brain's primary regulatory networks, focused on very low frequencies that have shown training effects in a single session in functional MRI [fmri]-based neurofeedback studies[28,29].

Unlike the early animal research, the senses of taste and smell are not commonly used, but 3 external feedback loops are commonly established using:

- Vision (typically a computer monitor with variable speed or size as feedback)
- Hearing (variation in feedback volume level)
- Touch (using vibro-tactile feedback[30] using a vibrating cushion or soft toy)



Non-directive approaches do not introduce directive processing into the external feedback loops. They present a 'pure' representation of the brain's activity back to itself via the feedback loop channels, without any concept of contingent reward, and any change is 'endogenous' or comes from within'[31].

NICE and Innovation

We question whether the "independence"[32] of the National Institute for Health and Care Excellence (NICE) operates in the best interests of tax payers or patients.

The independent committees of "experts" that review Clinical Guidelines are dominated by existing practitioners.

For example, the NICE Committee that reviewed the PTSD Clinical Guidelines[33] in 2016-218 had 13 members, including the Chair, who was a Director of Public Health. There were originally 4 lay members. The remaining professional membership was made up of 5 psychotherpists/psychologists, 2 psychiatrists, and one GP.

It is understandable that experienced professionals should be involved, but existing practitioners might also be considered to have a vested interest in maintaining the status quo and resisting disruptive innovations.

We note that one of the lay members, Andy Pike, resigned from the PTSD Guideline (update) Committee in June 2017. We have spoken to Mr Pike[34] and he volunteered that he resigned as a result of his concerns at the integrity of the committee membership in terms of declaring potential conflicts of interest, and the process.

The NICE review process is strongly facilitated by NICE staff, with up to 10 additional NICE staff taking part in the review meetings where analysis was presented to the Committee[35]. We can reasonably assume that from the published evidence review, Parts A-J which total 3,416 pages excluding appendices, much of which is a summary of the analysis performed, that there was minimal active review of the evidence by the Committee, and that they were largely guided by the NICE team.

As Calestous Juma points out in "Innovation and Its Enemies"[36], responses to new technologies depend on the extent to which they transform or reinforce established worldview, values or doctrines.

The idea of being able to remediate mental health issues with EEG biofeedback does not easily fit into the existing doctrine of psychiatric drugs that treat mental health disorders as imbalances in brain chemistry. Neither does it fit into the doctrine of psychotherapy that treats mental health disorders as behavioural responses that can be unlearnt.

We also know from Juma[36] that when economic factors underlie resistance to innovation, objections are usually expressed through non-market mechanisms, and the role of authority in either favouring the status quo or innovation is critical.

Evidence downgrading

One way in which NICE resists innovation is to downgrade the quality of evidence using subjective judgements.

A randomised controlled trial involves the participants being randomly allocated to (at least) two groups, one of which receives the experimental treatment, and a control group which doesn't receive the experimental treatment. The control group often receives no treatment, or waits until the control group have received the treatment before they receive the treatment, known as a "wait list".

The GRADE methodology (see Appendix) requires that randomised controlled trials are regarded as High Quality as a baseline.

There are many (100s of) randomised controlled trials of neurofeedback that demonstrate efficacy.

The GRADE methodology also provides the option to make *subjective* judgements on a number of factors, and consequently downgrade the evidence. Although the methodology authors make it clear that these are subjective judgements, and that such judgements should be explicitly declared, NICE's reports do not make it clear exactly what these judgements are, nor that they are subjective.

A key area where NICE make subjective judgements to downgrade the quality rating of randomised controlled trials is due to the "risk of bias".

There is a risk of performance bias and/or detection bias shared by all studies that don't have a double-blinded placebo control 'sham' arm. Performance bias is the risk that the participants and/or the experimenters know they received the experimental treatment rather than the control, and that this knowledge *could* have a bearing on the outcome, rather that the treatment itself [37]. Detection bias is the risk that when conducting the outcome assessment, the assessors know whether the participant had the experimental treatment rather than the control, and that this knowledge *could* have a bearing on the outcome, rather than the treatment itself.

The literature is clear that a good solution to the problem of bias is the use of indistinguishable placebo tablets, or a sham control procedure that is indistinguishable from the experimental one, known as a double-blinded placebo controlled trial.

Single-blinded means that either:

i. The subjects do not know whether they are receiving the real treatment or the sham/fake. By comparing the difference in response between those receiving the real vs the sham, the placebo effect can effectively be taken out of the analysis.

ii. The personnel conducting the trial do not know receiving the real treatment or the sham/fake. This can remove the risk that the assessors' judgement of the outcome is biased by their knowledge of the treatment received, and the risk that the experimenter acts in a way that means the subject is 'unblinded', i.e. Realises which treatment they have received.

Double-blinded means that the subjects *and* the experimenters/assessors do not know who is receiving the real or sham treatments.

For vaccines or medications, double-blinding can be achieved relatively easily as long as the 'sham' looks and feels like the real treatment.

For example, with the Pfizer COVID19 vaccine the sham was a saline solution; for the Oxford vaccine the sham was the meningitis vaccine.

For non-pharmacological interventions, there are challenges with double-blinded placebos:

i. It can be very difficult or impossible to create a sham.

   For example, no-one would suggest performing 'sham' psychotherapy, where the therapist conducted a sham session, where they pretended to provide therapy but were really faking it.

   There are significant technical barriers to creating an experiment where neurofeedback therapy could be conducted as a sham whilst both the practitioner and the client believe they are delivering/receiving the real thing. It would require especially developed software.

ii. It can also be much harder to recruit participants. It is significantly more effort than popping a pill once a day, and the asking people to attend 20 sessions of what might be a placebo is a significant ask.

For these reasons, the literature recognises that "blinding may not be feasible in many non-drug trials, and it would not be reasonable to consider the trial as low quality because of the absence of blinding"[38].

NICE's practice of downgrading of non-pharmacological randomised controlled trials appears to be at odds with the literature. Guidelines that it would be unreasonable to downgrade evidence in this way[38], and guidelines that any such subjective judgements should be declared as such[62], and explicitly justified[62], seem to be routinely ignored.

Appendix A of Ref 40 p377 includes the following explanation of the Review Strategy (our *emphasis*):

> "For risk of bias, outcomes will be *downgraded* if the randomisation and/or allocation concealment methods are unclear or inadequate. Outcomes will also be *downgraded* if no attempts are made to blind the assessors or participants in some way, i.e. By either not knowing the aim of the study or the result from other tests. "

This de-facto downgrading is inconsistent with the literature.

It could be argued that NICE deliberately misrepresent subjective judgements as objective evidence reviews.

Chicken & egg bind – resistance to new treatments as they are not widespread

Despite the obvious ramifications on innovation, the committees seem comfortable perpetuating the "chicken & egg" dichotomy of being unwilling to recommend an intervention that is not in widespread use.

Two examples follow, from our experience expending significant effort engaging with NICE's consultation process on ADHD and PTSD.

The conclusions were similar, i.e. They were not going to recommend neurofeedback therapy as the evidence was regarded as low quality (see above), and the committee did not have clinical experience of it and/or not many people were offering it.

The conclusions of the ADHD review[39] were (our *emphasis*):

> "Other interventions (for example neurofeedback and attention/memory training) did show clinically important benefits for some outcomes including total ADHD symptoms as rated by parents and ADHD inattention and hyperactivity symptoms as rated by parents and teachers. However, the committee noted that many of these benefits were generally supported by smaller studies and lower quality studies than for parent training and were less consistent. The committee *took into account current practice and their clinical experience* and agreed that the current evidence base for these other interventions was insufficient to make specific recommendations for their use."

The conclusions of the PTSD review[40] were (our *emphasis*):

> "The committee discussed the evidence for biofeedback and neurofeedback and noted that benefits observed for self-rated PTSD symptomatology did not reach statistical significance for clinician-rated PTSD symptomatology or remission.

> Furthermore, there was no evidence of long-term follow-up and concerns about the generalisability of results (all multiple incident index trauma, predominantly military combat-related).
>
> Taking into account these limitations of the evidence, and *bearing in mind that such interventions are not in routine clinical practice and would require significant resources and training, the committee did not think that a recommendation was appropriate*."

In summary, although participants believed the therapy worked, this was deemed less important than clinicians ratings, and the committee decided a recommendation was not "appropriate" because existing practitioners don't know how to deliver it.

Return on Investment and Health Economics Analysis

This analysis is based on several existing sources, together with some working assumptions*.

Basis of Estimate:

8.3% of population experiencing 4+ aces[41]
£287 late intervention cost average per person in UK per annum[42]
£3,458 late intervention cost per person per annum suffering 4+ aces (£287/8.3%)

81 year average lifespan UK
-12 average lifespan reduction assumed for 4+ ACE sufferers[41]
69 years lifespan assumed for 4+ ACE sufferers
14 age at which 4+ aces suffered*
55 number of life years with 4+ ACE sufferers
22 average age at which neurofeedback therapy is provided

£191,000 lifetime cost of late intervention of 4+ ACE sufferers (55 x £3,458)
£85,000 Net Present Value of cost of late intervention (Discount Factor 3.5% pa)

We have assessed cost and effectiveness in 2 ways: A simple model based upon our private client experience where non-attendance is a negligible factor; and Decision-tree based models that allow a more nuanced analysis. We begin with the simple model.

Cost of Advanced QEEG Brain Mapping and 40 sessions of neurofeedback therapy: £3,840
Success rate at complete remediation: 80%*
Cost per successful intervention: £4,800.

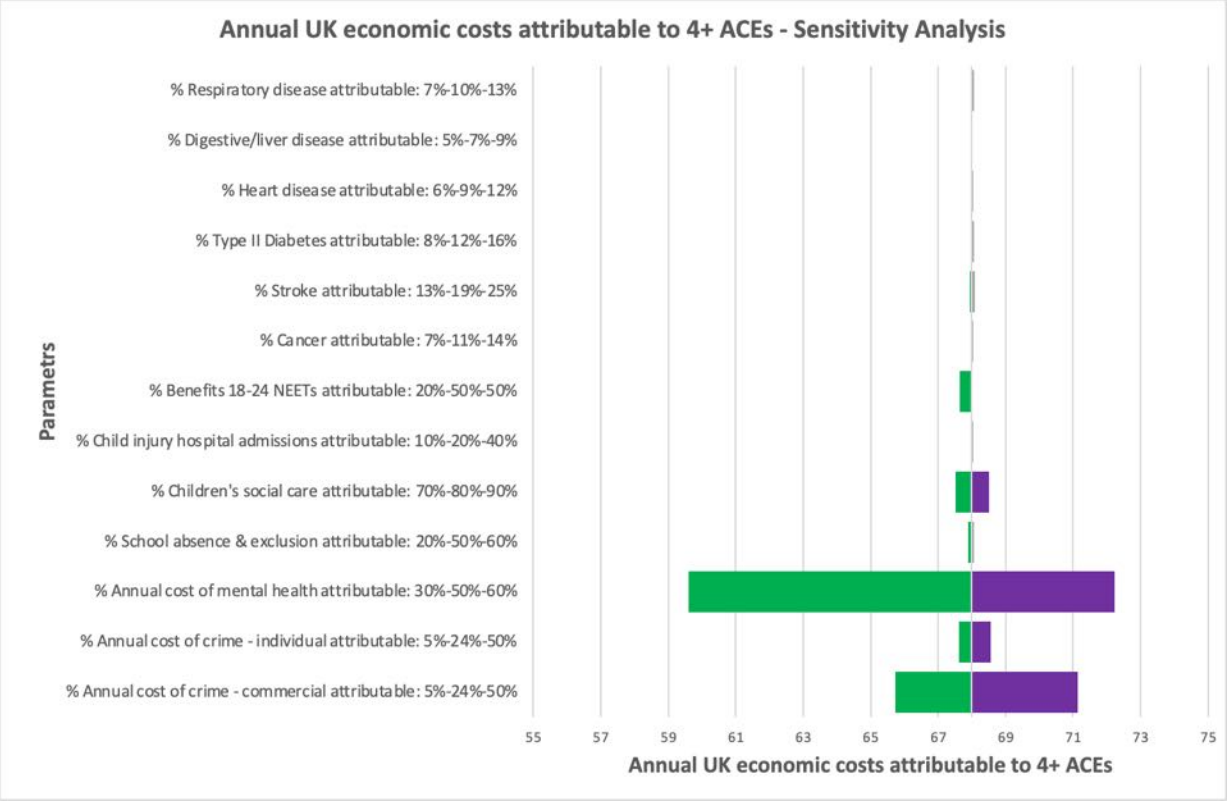
Return on Investment: £85,000 - £4,800 = £80,000 per client/patient, £80m per 1000.

This analysis is simple, but is believed to be conservative.

We have separately quantified the cost of unmitigated 4+ aces at £68bn per annum from a 'drains-up' analysis of the costs of crime, NEETS, children's care, mental health and chronic disease.

With 5.4m of the population suffering 4+ aces, this equates to an unmitigated 4+ aces cost of £12,500 per person per annum. This suggests the roi above may be understated by > 3 times.

The sensitivity analysis for the figure of £68bn is overleaf. It can be seen that the estimate is most sensitive to mental health costs. The baseline figure assumes that 50% of mental health costs can be attributed to 4+ aces. The sensitivity analysis demonstrates that if this figure was reduced to 30% the total figure will still be > £59bn pa.



Health Economics

When the NICE Guidelines for Adult PTSD were reviewed in 2018[43], no economic analysis was performed for Neurofeedback Therapy.

One reason was "bearing in mind that such interventions are not in routine clinical practice and would require significant resources and training, the committee did not think that a recommendation was appropriate." (Ref 40, p.367).

We have conducted a further analysis using a simplified version of the NICE methodology, to enable comparison with other interventions. We have been grateful for the guidance of Dr Mathew Taylor, Director of the York Health Economics Consortium in this work.

NICE health economic analyses are based upon comparing changes in Quality Adjusted Life Years (QALYs) with differences in costs of respective interventions.

Quality Adjusted Life Years

QALYs are based upon Utility Scores linked to Health States. A fully healthy life equates to 1 QALY per year. Death is 0.

NICE's assessment of the evidence of health-state utility data for PTSD included 3 studies.

For the QALY analysis, NICE chose an Australia and New Zealand study[44] that compared the health states of those had a 12-month diagnosis of PTSD but without a current (30- day) diagnosis, who had received CBT, with those with a 12-month diagnosis of PTSD who had not been receiving treatment.

These health utilities reflect the effectiveness of CBT, and those without a PTSD diagnosis still had a relatively low utility score of 0.63 (male) - 0.64 (female). From Ref 44 Table 197):

Health-state	Utility Scores		
	Male	Female	Mean
PTSD-free	0.63	0.64	0.635
With PTSD	0.54	0.57	0.555

NICE decided not to use the utility scores from another study that showed a non-PTSD health utility of 0.87[45], on the basis that these reflected people who may not have suffered PTSD, and "utility values in people who have never had PTSD are expected to be higher than those in people who have remitted from PTSD[46]."

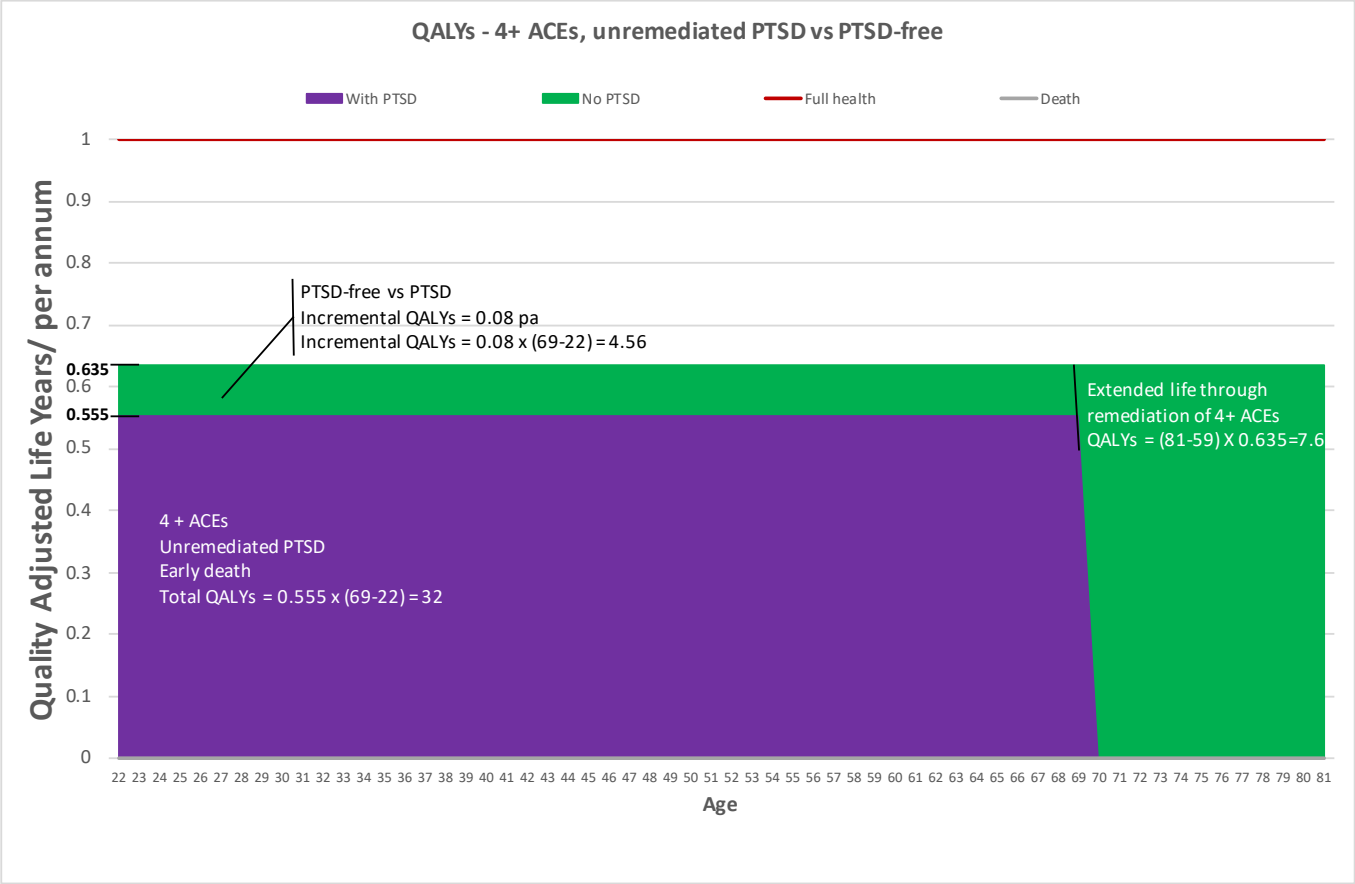
Whilst this is logical, our proposition is that early intervention will avoid the long-term health deterioration as a result of the allostatic load of the chronic stress of PTSD, and so such a health utility is very possible upon remission from PTSD. A health utility of 0.87 would be a QALY increment 300% greater than that assumed: (0.87 – 0.555)/(0.635 – 0.555) = 0.315/0.08 = 3.94.

For the sake of our analysis, we have assumed 50:50 male:female ratio, giving mean Utility Scores of 0.635 without PTSD and 0.555 with PTSD, i.e. A difference of 0.08 Quality Adjusted Life Years (QALYs) for every year of life.

Assuming that the intervention occurs at the age of 22, we can calculate the impact that successful neurofeedback therapy has on QALYs:

	Years	QALYs
No intervention – with PTSD	69-22 = 57	57 x 0.555 = 32
Remediation of PTSD through Neurofeedback	69-22 = 57	57 x 0.635 = 36
Incremental QALYs	57	57 x 0.08 = 4.6
Extended life through remediation of 4+ aces	81-69 = 12	12 x 0.635 = 7.6

This is illustrated overleaf.



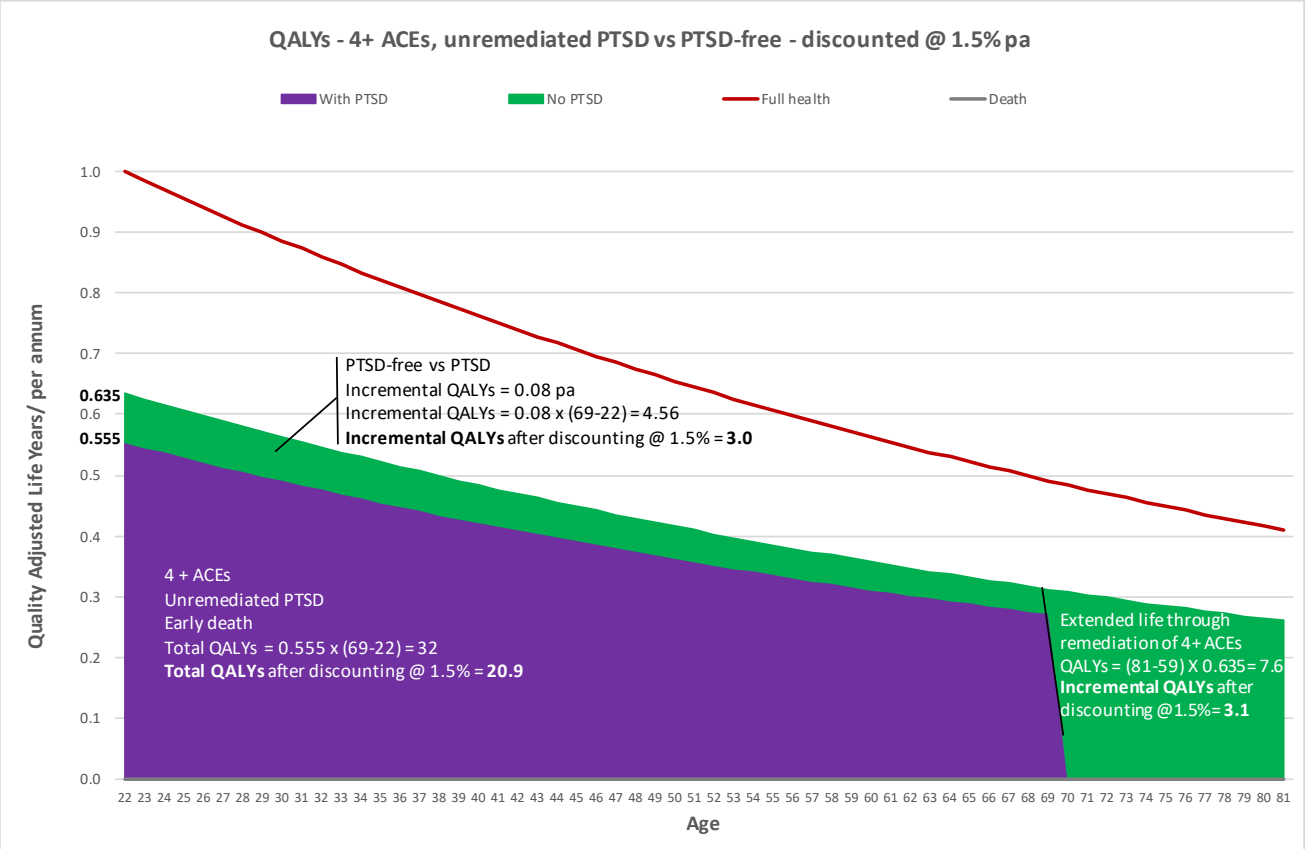
Somewhat controversially, NICE expect future QALYs to be discounted. Historically this has been at 3.5% per annum, though in 2013 NICE changed the guidance to allow for long-term benefits (longer than 30 years) to be modelled at 1.5% pa[47].

Asst Prof James O'Mahony of Trinity College, Dublin and Asst Prof Mike Paulden of University of Alberta are [48]critical of this change to so called "differential discounting", claiming it was only made in order to ensure a favourable cost-effectiveness ratio for a children's cancer drug.

We also note that NICE are considering[49] changing the default discount rate to 1.5%. The following table and graph show the impact of discounting at 1.5% pa:

	Years	QALYs	Discounted QALYs
No intervention – with PTSD	69-22 = 57	57 x 0.555 = 32	38 x 0.555 = 20.9
Remediation of PTSD through Neurofeedback	69-22 = 57	57 x 0.635 = 36	38 x 0.635 = 23.9
Incremental QALYs	57	57 x 0.08 = 4.6	3.0
Extended life through remediation of 4+ aces	81-69 = 12	12 x 0.635 = 7.6	4.8 x 0.635 = 3.1

Additional QALYs as result of remediation of PTSD	3.0
Additional QALYs as result of extended life	3.1
Total additional QALYs including extended life	6.1



The two key calculated measures are Incremental Cost-Effectiveness Ratio and Net Monetary Benefit.

Incremental Cost-Effectiveness Ratio (IECR) = ΔC/ΔE where ΔC is the difference in total costs between two interventions and ΔE is the difference in effectiveness in QALYs.

One comparison point is the cost of "No treatment". NICE calculate[50] that adults with PTSD cost the NHS an average of c. £1,000 per annum more than those who don't.

Over our period of analysis, for those with un-remediated PTSD as a result of 4+ aces (55 years), this equates to £55,000, which after discounting at 3.5% pa is equivalent to £24,500 current cost.

=> ΔC = £4,800 - £24,500 = - £19,700, i.e. The intervention costs less than no treatment.

Including extended life, ICER = -£19,700/6.1 = -£3,230/QALY which is well below the NICE lower cost effectiveness threshold of £20,000/QALY.

If the extended life is excluded, ICER = -£19,700/3.0 = -6,567/QALY, still well below the NICE lower threshold.

Net Monetary Benefit (NMB) = E x λ – C where E is effectiveness (number of QALYs), C are costs, and λ is the level of the willingness-to-pay (WTP) per unit of effectiveness, set at the NICE lower cost effectiveness threshold of £20,000/QALY.

NMB = 6.1 x £20,000 - £4,800 = £117,000/person.

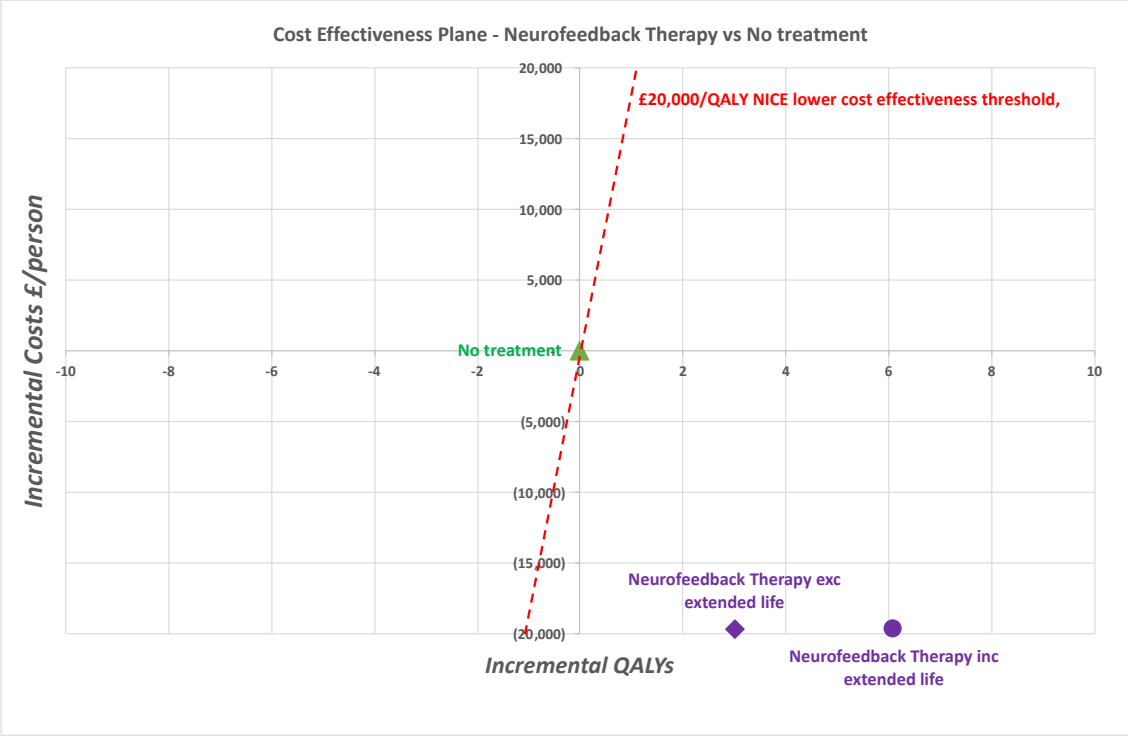
If the extended life is excluded, NMB = 3.0 x £20,000 - £4,800 = £55,200/person.

Cost Effectiveness Plane

A Cost Effectiveness Plane plots comparative (incremental) costs and QALYs for a candidate intervention relative to a reference intervention. Those interventions that cost less and add QALYs should be accepted. Interventions that cost more but add QALYs will be accepted subject to the willingness-to-pay (WTP) per unit of effectiveness, set at the NICE lower cost effectiveness threshold of £20,000/QALY.

In the example below, Candidate Intervention A would be accepted, Candidate Intervention B would be rejected:

Plotting the analysis of Neurofeedback therapy vs. No treatment on the cost effectiveness plane shows that Neurofeedback costs less and adds QALYs, and on that basis would be accepted:



Comparison with other interventions

Cost Effectiveness Planes often express the data per 1000 patients, i.e. Both incremental costs and incremental QALYs are multiplied by 1000.

The graph below adopts this convention, and also shows how the interventions assessed by NICE would be displayed on this scale:

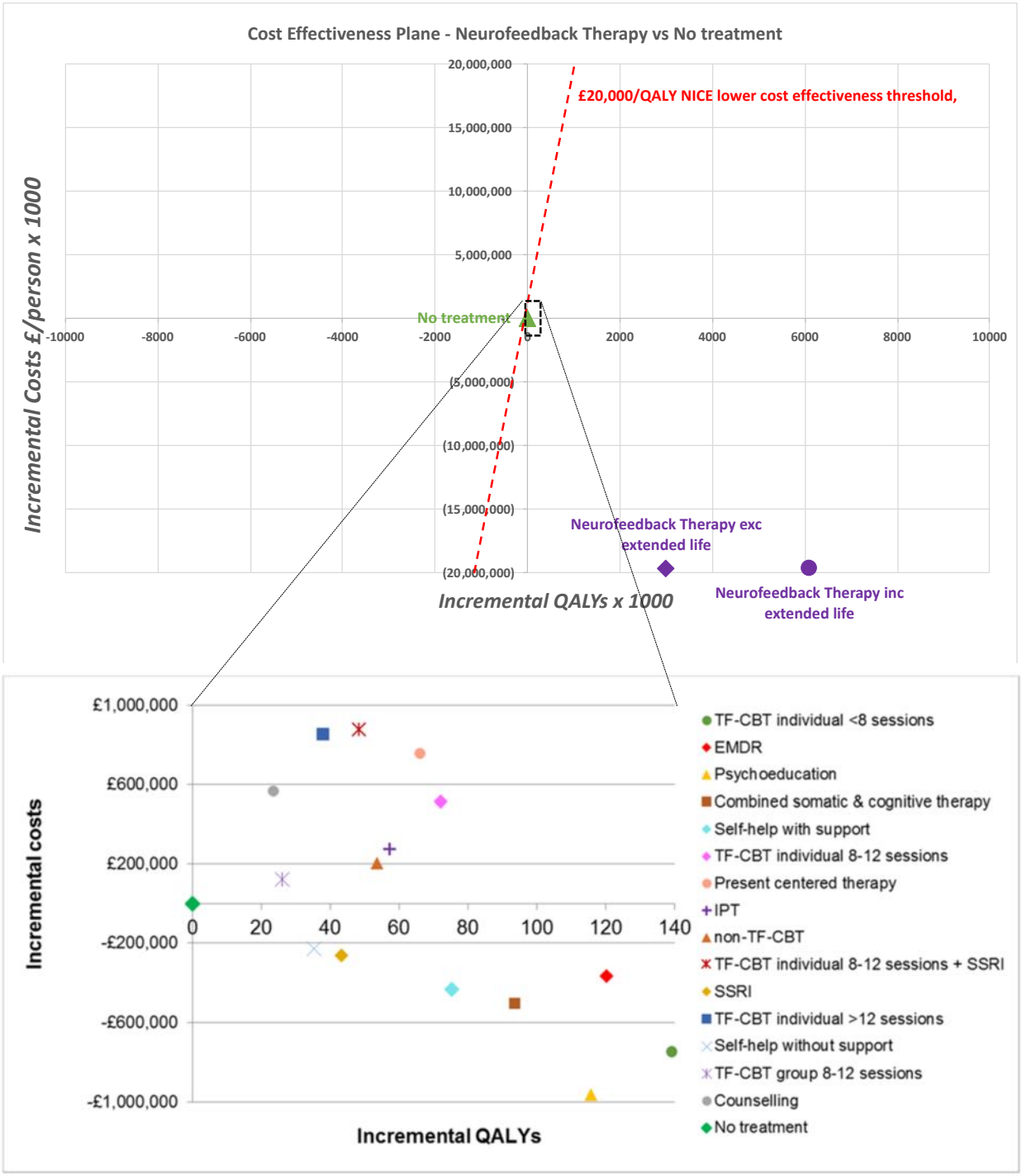


Figure 701 from Ref 50

The obvious question is why is there such a disparity between the NICE analysis and our analysis?

Constraint on Benefits of 3 years

Following discussion with an expert in Health Economics[51] it became apparent that NICE's analysis restricted the benefits to 3 years.

PTSD is a chronic condition, severely affecting the lives of many of those suffering. As described earlier, the allostatic load caused by chronic stress often leads to other conditions and early death.

Consequently, our healthcare economics modelling has taken a long-term view, and we have quantified the cost effectiveness of our neurofeedback therapy programme significantly below the NICE cost effectiveness threshold of £20,000/QALY.

The long-term nature of PTSD has been quantified by evidence[52] quoted by NICE's evidence review[40] that identifies that *median time to remission from PTSD is 14 years*, with *37% having symptoms 30 years after onset*.

The rationale for limiting the analysis to 3 years is unknown, is inconsistent with academic evidence and clinical experience, and raises questions of credibility and validity.

This constraint has a major effect on the health economic analysis, severely limiting the incremental QALYs possible within 3 years, and impacting the Net Monetary Benefit.

Net Monetary Benefit (NMB) = E x λ – C where E is effectiveness (number of QALYs), C is costs, and λ is the level of the willingness-to-pay (WTP) per unit of effectiveness, set at the NICE lower cost effectiveness threshold of £20,000/QALY.

For Neurofeedback therapy, NMB = 6.1 x £20,000 - £4,800 = £117,000/person.
If extended life is excluded, NMB = 3.0 x £20,000 - £4,800 = £55,000/person.

If this analysis is artificially constrained to 3 years worth of benefits, then there is no QALY benefit from life extension, and NMB = 1.84* x £20,000 - £4,800 = £32,000/person.

*QALYs = [QALYs with PTSD + (QALYs without PTSD – QALYs with PTSD) x % remediation] x 3yrs inc. Discount factor
= [0.555 + (0.635-0.555) x % remediation] x (1 + (1-3.5%) + $(1-3.5\%)^2$)
= [0.555 + 0.08 x % remediation] x 2.8962 = [0.555 + 0.08] x 2.8962 = 1.839

Despite this constraint, Neurofeedback therapy compares favourably with other interventions assessed by NICE.

Table 204 from Ref 50 lists the assessed interventions in order of calculated NMB. We have inserted the data for Neurofeedback under this constraint:

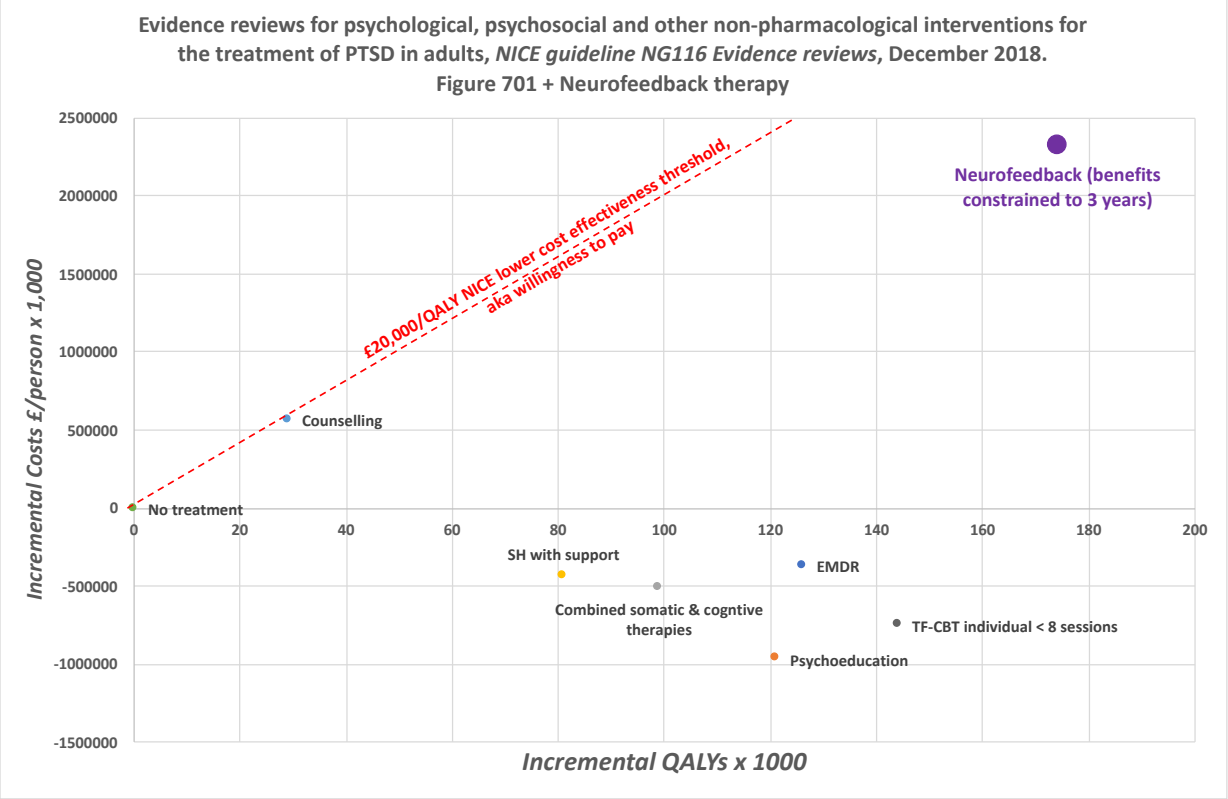
Intervention	Mean per person			NMB £/ person
	QALY	Inter cost £	Total cost £	
TF-CBT individual <8 sessions	1.809	541	1,722	34,467
EMDR	1.791	747	2,103	33,709
Psychoeducation	1.786	109	1,506	34,214
Combined somatic & cognitive therapies	1.764	358	1,964	33,314
SH with support	1.746	266	2,036	32,876
Neurofeedback therapy	1.84		4,800	32,000

TF-CBT individual 8-12 sessions	1.742	1,181	2,983	31,865
Present-centred therapy	1.736	1,373	3,228	31,498
IPT	1.728	810	2,747	31,805
non-TF-CBT	1.724	706	2,676	31,800
TF-CBT individual 8-12 sessions + SSRI	1.719	1,326	3,348	31,022
SSRI	1.714	145	2,209	32,065
TF-CBT individual >12 sessions	1.708	1,205	3,325	30,841
SH without support	1.706	98	2,241	31,873
TF-CBT group 8-12 sessions	1.696	362	2,592	31,334
Counselling	1.694	785	3,038	30,838
No treatment	1.670	0	2,471	30,935

Extract of Table 204 from Ref 50 with 3-year constrained data on Neurofeedback inserted

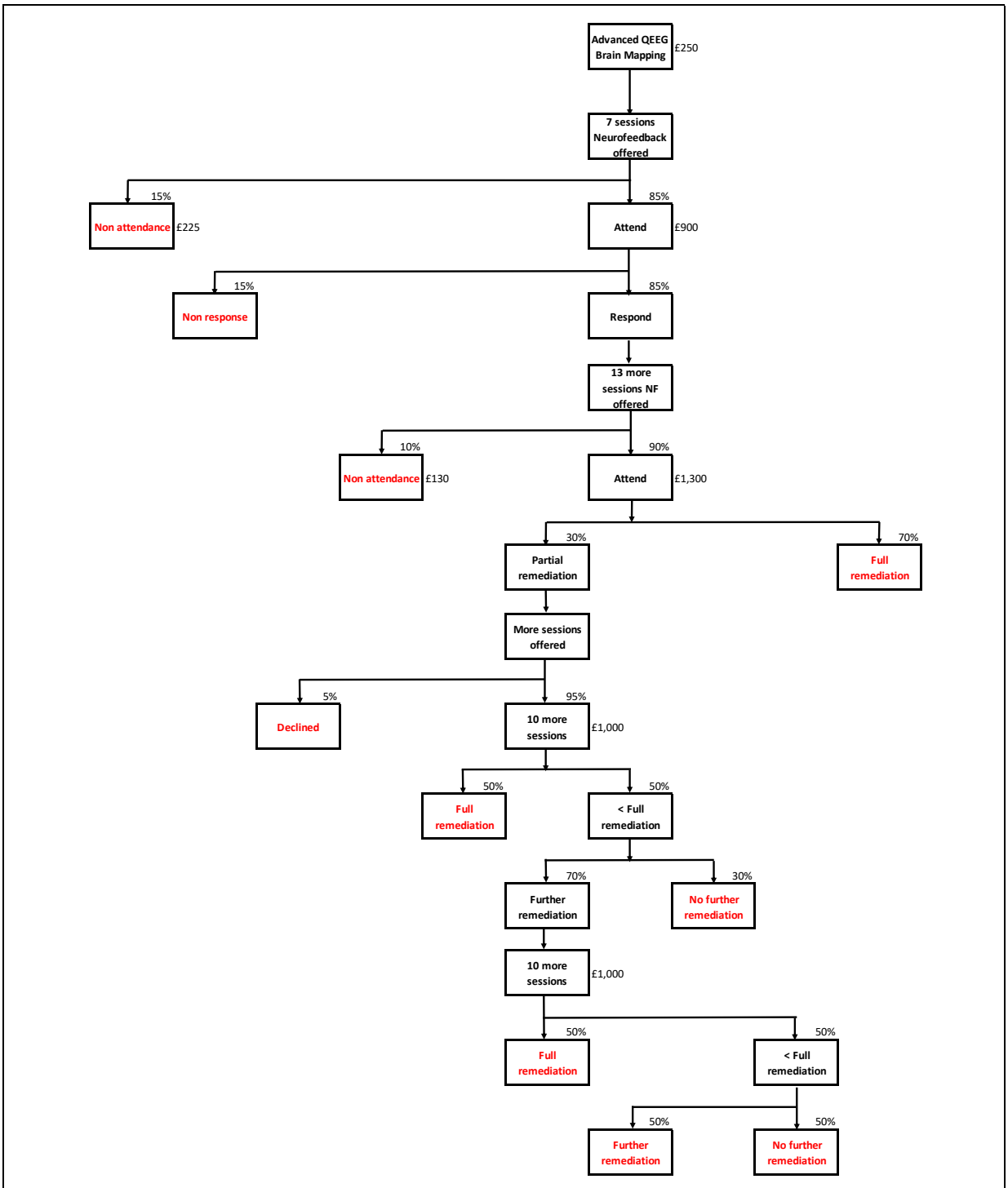
This comparison on the cost effectiveness plane relative to No treatment illustrates that Neurofeedback therapy compares favourably with NICE-approved interventions.

Whilst the incremental cost is greater than No treatment, it is clearly on the right side of the willingness-to-pay (WTP) threshold:



Decision Tree Model

Decision trees enable a more nuanced assessment of the pathway and modelling of variability and uncertainty. The decision tree we have developed for Neurofeedback therapy is shown below. It introduces possibilities of non-attendance, and also models a staged approach to adding sessions, up to a maximum of 40 sessions, rather than the simple model which assumes that everyone will receive 40 sessions.



Total %	15.00%	12.75%	0.98%	7.23%	9.27%	3.24%	1.62%	2.78%	1.62%	45.52%	**100.00%**
Total Cost	£475	£1,150	£2,450	£1,280	£3,450	£4,450	£4,450	£3,450	£4,450	£2,450	
Remediation	0	0	0	0	100%	100%	75%	50%	60%	100%	
% x Cost	£71	£147	£24	£92	£320	£144	£72	£96	£72	£1,115	**£2,154**
% x Remediation	0.0%	0.0%	0.0%	0.0%	9.3%	3.2%	1.2%	1.4%	1.0%	45.5%	**62%**

A deterministic analysis assigns a fixed probability estimate at each decision stage. The results are shown in the bottom rows, and correspond to each of the end-stages in red above.

With the inclusion of the risk of non-attendance, the average (mean) remediation is adjusted to 62%, and with the staged approach to session management, the average mean cost is adjusted to £2,154.

The revised QALYs are:
QALYs = [0.555 + 0.08 x % remediation] x 2.8962
= [0.555 x 0.08 x 62%] x 2.8962
= 1.751

We can insert these figures into Table 204 of Ref 50 to show that the NMB improves:

Intervention	Mean per person			NMB £/ person
	QALY	Inter cost £	Total cost £	
TF-CBT individual <8 sessions	1.809	541	1,722	34,467
EMDR	1.791	747	2,103	33,709
Psychoeducation	1.786	109	1,506	34,214
Combined somatic & cognitive therapies	1.764	358	1,964	33,314
SH with support	1.746	266	2,036	32,876
Neurofeedback therapy	1.751		2,154	32,867
TF-CBT individual 8-12 sessions	1.742	1,181	2,983	31,865
Present-centred therapy	1.736	1,373	3,228	31,498
IPT	1.728	810	2,747	31,805
non-TF-CBT	1.724	706	2,676	31,800
TF-CBT individual 8-12 sessions + SSRI	1.719	1,326	3,348	31,022
SSRI	1.714	145	2,209	32,065
TF-CBT individual >12 sessions	1.708	1,205	3,325	30,841
SH without support	1.706	98	2,241	31,873
TF-CBT group 8-12 sessions	1.696	362	2,592	31,334
Counselling	1.694	785	3,038	30,838
No treatment	1.670	0	2,471	30,935

Extract of Table 204 from Ref 50 with 3-year constrained data on Neurofeedback inserted

Probabilistic analysis
We have also performed a probabilistic analysis using a Monte-Carlo simulation. A probabilistic analysis assigns probability distributions to input variables.

Each probability decision stage within the Decision Tree was modelled by a Beta distribution, as recommended by Ref 53. The parameters for the Beta distribution, $\propto$ and β, were calculated using the deterministic model parameter as the mean (m), with the Standard Deviation (s) set at 10% of the mean:

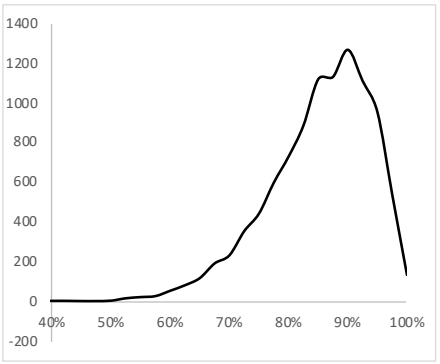
$$\propto = \frac{m^2(1-m)}{s^2} - 1 \qquad \beta = \frac{m(1-m)^2}{s^2}$$

For example, in the Decision Tree's first decision point, after 7 sessions of Neurofeedback offered, the probability of the outcome "Attend" with a deterministic parameter of 85%, was modelled using a Beta distribution using the parameters:

M = 0.85, s = 0.85 x 10% = 0.085

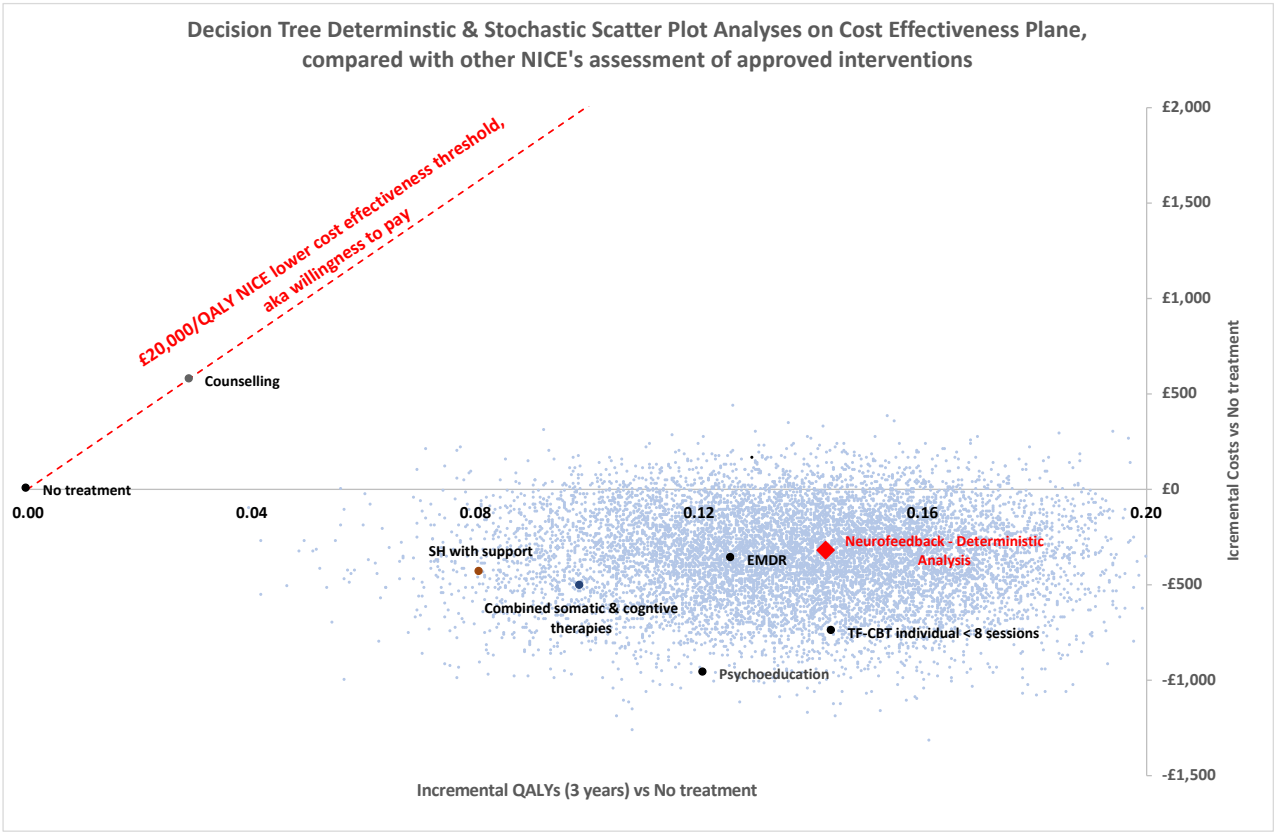
$\propto = 0.85^2.(1\text{-}0.85)/0.085^2 - 1 = 14$, $\beta = 0.85.(1\text{-}0.85)^2/0.085^2 = 2.65$

The resultant distribution for this decision stage is shown below:



This is repeated for all the decision points. A simulation is then run many times, in this case 10,000 times, and the resultant multiple outputs provide a probability distribution of outcomes.

The resultant scatter-plot diagram shows 10,000 iterations on the cost-effectiveness plane, illustrating that the probabilistic analysis indicates that willingness to pay is unchallenged by this sensitivity analysis:



We conclude that Neurofeedback therapy stands up to scrutiny on health economic grounds, and is as cost effective, or more cost effective, than existing approved interventions. Assumptions have been made in reaching this assessment, but the sensitivity analysis has demonstrated that a willingness to pay assessment is not sensitive to a wide range of variability.

This is notwithstanding the constraints imposed by NICE, including artificially restricting the benefits assessment to 3 years, choosing a pessimistic health utility score for PTSD recovery, and discounting of future QALYs.

Without these constraints, the Net Monetary Benefit would be more than 13 times greater, i.e. In excess of £400,000 per person on average.

Neurofeedback therapy offers the NHS a significant opportunity to improve outcomes and reduce costs, particularly for those who will not engage in talking therapies or reimagine the trauma.

Appendix A: Applied Neuroscience Solutions Background & Team

Applied Neuroscience Solutions Ltd, trading as braintrainuk since 2013, are the only multi-disciplinary, multi-modality neurofeedback therapy practice in the UK. We lead the UK in terms of size, geographic spread and thought leadership.

We have successfully delivered programmes of neurofeedback therapy to 100s of clients, both adults and children. We have treated many clients with a history of childhood trauma.

Surrey County Council's Virtual School contracted us to provide our services to Looked After Children, and we are in discussions with several other Local Authorities and the Adoption Support Fund to make our services more widely available.

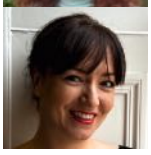
Our team of staff and advisors include:

Zuzana Radacovska MA – Neurofeedback Practitioner
Degree in psychology, worked in juvenile justice system, braintrainuk practitioner for 5 years. Experience using bio and neurofeedback techniques for peak performance with athletes and executives.

Dr Marina Chirco MD – Medical Advisor
GMC-registered NHS Medical Doctor, post-doctorate studies in Neurofeedback, Psychoneuroendocrinimmunology, Acupuncture, NAET.

Agnieszka Sosnecka MSc (Cog Neuro) – Neurofeedback Practitioner & Consultant
Cognitive Neuroscientist specialised in Clinical Psychology & Psychopathology, phd student creativity in autism.

Jo-Anne Buttle MSc – Neurofeedback Practitioner
Educational Psychologist, msc Educational Psychology, HCPC Registered. Extensive experience working with local authorities and private practice.



Anna Dybul MSc – Neurofeedback Practitioner
Anna has a particular interest in the use of music as a therapeutic intervention for speech disorders, and the application of Neurofeedback to peak performance.

Kirsten Antoncich MSc – Neurofeedback Practitioner
Masters in Integrative Psychotherapy, has taught English & Psychology in SEN, run a mental health service in the North East of England, and pastoral support service to schools.

Helen Wagstaff – Recruitment Consultant
Freelance recruitment professional, experience with wide range of industries and blue-chip organisations, specialist in innovative & unusual roles.

Stuart Black BSc (Eng) MSc CEng MIET – Founder & Managing Director
Chartered Engineer, 30 years experience with blue chip organisations including BAE SYSTEMS, General Dynamics, Bupa, Centrica.

Complex international product development & board-level change and interim Management experience. Accountable for £multi-million P&Ls. 4 years as Executive Director at Cromwell Hospital in London. Board-level advisor to NHS Trusts.

Special Guardian to 3 children of a friend who died in 2017. Family Rights Group Kinship Panel Member & Trustee. Chair of North West Surrey Foster Care Association.

Sairah Shah BA MA PGCE – Senior Education Consultant
Graduated in History in History (Asia and Africa) from the University of London's School of Oriental & African Studies where she also gained a Masters in History.

Sairah has taught History and been a successful education leader in a variety of mainstream contexts in including 5 secondary schools, an FE College and local authority for 20 years.

Dr David A Kaiser PhD – Scientific Advisor
Doctor in Psychology and Neuroscience. Developer of SKIL software for use in neurotherapy and brain function assessment which relies on functional connectivity and hemodynamics.

Editor of the Journal of Neurotherapy for a decade, fellow of the International Society for Neurofeedback and Research, President of the Neurofeedback Division of the Association for Applied Psychophysiology and Biofeedback, and has taught neuropsychology and neuroscience courses at various colleges. Widely published.

Marcia Saul BSc MSc – Postgraduate Researcher, Bournemouth University
Bsc in Biology with Psychology, msc in Computational Neuroscience. Marcia is conducting doctorate research defined and sponsored by braintrainuk into the use of neurofeedback with multiple participants (aka hyperscanning) to address social anxiety.

Dr Fred Charles BSc MSc PhD – Deputy Head of Department in Creative Technology, Bournemouth University
BSc in Computer Science, Master's degree in Computer Aided Graphical Technology Applications, PhD Computer Science.

Fred is one of Marcia's supervisors, and co-authored published research[54] on a randomised, placebo-controlled trial using neurofeedback to down-regulate limbic activity to reduce pain symptoms in fibromyalgia sufferers.

Dr Xun He BSc PhD – Senior Lecturer in Psychology, Bournemouth University
BSc in Biology, PhD in Biophysics. Xun is Marcia's second supervisor. An experimental psychologist and social neuroscientist, studying the behaviour and neural underpinnings of social attention and social perception.

Xun's main research question is how human attention and perception performance is shaped by social interactions such as joint action and shared attention, and whether social behaviour can be improved by neurofeedback? Expert in the electroencephalography (EEG) technique (including hyperscanning EEG) and Head of the Bournemouth EEG Lab.

Appendix B: Discovery of EEG Biofeedback

In 1968 Barry Sterman, who was studying localized EEG patterns in relation to specific behaviors in cats, demonstrated the use of operant conditioning to train cats to generate a distinctive brainwave rhythm over the motor cortex, the part of the brain associated with movement control, when rewarded with milk[55].

This pattern, in the frequency range 12-20Hz, was termed the 'sensorimotor rhythm' (SMR).

Months later, unrelated research[56] funded by the space race into the effects of rocket fuel (hydrazine) involved injecting rocket fuel into a number of cats and observing the results as all the cats cried, vomited, salivated, and after an hour, most of them had a seizure.

Initially Sterman could not understand why a minority of the cats had not had a seizure after 1 hour, until it was realised that these seizure-resistant cats were the only ones that had taken part in the previous study to condition the cats to generate enhanced SMR.[57] The operational conditioning of the SMR had been transferred to immunity to seizures.

This experiment was repeated and then extended to primates and later humans, including an 'double-crossover' study design[58] on epileptic patients where part of the experimental protocol was to *reverse* the direction of operant conditioning at 12-15Hz unknown (blinded) to the subjects, which *increased* the incidence of seizures.

Examining the underlying neuroscience, the 'sensorimotor rhythms' (SMR) are generated within the somatosensory nuclei of the thalamus, relayed to the somatosensory cortex (where they can be picked up via scalp electrodes) and to the nucleus reticularies thalami, which responds with a similar burst, at the same time releasing the neurotransmitter GABA, which causes the process to begin again[59,53]. This back-and-forth rhythm controls excitability and enables control over motor function.

Hydrazine interferes with the synthesis of GABA[53], effectively abolishing these EEG rhythmic patterns, increasing cortical and thalamic excitability, and making the brain vulnerable to seizure when stimulated[53].

Therefore it can be concluded that the strengthening of the SMR rhythms through conditioning either increased GABA synthesis, up-regulated GABA receptors, or facilitating another inhibitory process[60].

Appendix C: NICE Evidence Assessment Methodology

Appendix F of the PTSD Non-Pharmaceutical Evidence Review[40] p841-1060 includes GRADE Tables for the evidence considered. The GRADE (Grading of Recommendations, Assessment, Development and Evaluations) methodology[61] provides a method to assign a level of quality to the evidence. GRADE offers 4 levels of evidence quality:

- High
- Moderate
- Low
- Very low

GRADE requires that evidence from randomised controlled trials starts as High and is upgraded or downgraded as other factors are considered.

It is important to note that GRADE assessments are subjective - they cannot be implemented mechanically[61]. Because of this subjectivity, GRADE recommends that the subjective judgements made in the assessment are very clearly stated[62] alongside any evidence assessments.

Factors for downgrading are:

- Risk of bias, which best practice guidelines[63] define as risk of:
    - Selection bias - was the randomisation truly random, was the mechanism hidden?
    - Performance bias - were participants and/or researchers blind as to the allocated intervention?
    - Detection bias - was the outcome assessment blind to the allocated intervention?
    - Attrition bias - is the outcome data complete, is participant drop out or exclusion reported?
    - Reporting bias – was reporting selective?
    - Other bias
- Imprecision[64] – Can we be confident that in 95% of cases, the intervention will provide a clinically worthwhile outcome? Is the sample size and number of events sufficient to make this estimate robust?
- Inconsistency – Is there inconsistency in relative effect, e.g. two studies suggesting benefit and two studies suggesting harm.[65]
- Indirectness – Do the i population, intervention, or outcomes differ from those in which we are interested? Or is there a lack of direct comparative studies that compare, for example intervention A with intervention B, instead relying on comparing effects of A vs control with B vs control.[66]
- Publication bias – Have negative studies been under-published or positive studies over-published?

Factors for upgrading[67] are:

- When a large magnitude of effect exists.
- When there is a dose–response gradient, i.e. There is a correlation between the doseage and the response.
- When all plausible confounders or other biases increase confidence in the estimated effect.

Appendix D: Previous Correspondence with Government/Military

The following correspondence is attached:

2020 correspondence with Children's Minister
2019 correspondence with Chair of HoC Defence Committee
2016 correspondance with Medical Director Defence Medical Services

BrainTrainUK
Changing Lives With Neurofeedback

Vicky Ford MP
Parliamentary Under Secretary of State for Children and Families
Department for Education
20 Great Smith St
Westminster
London
SW1P 3BT

11 November 2020

Opportunity to reduce effects of childhood trauma and improve adoption outcomes

Dear Vicky,

The cost to society of childhood trauma is significant. We have estimated the cost to UK society of unremedied Adverse Childhood Experiences at £68bn per annum[1].

I am very aware both professionally and personally of the effects of trauma on children.

My partner and I are Special Guardians of 3 children of a friend who died in 2017, I am also a Trustee/Director of the Family Rights Group, and was at the launch of the Kinship Care report in September.

I'm also founder of Applied Neuroscience Solutions Ltd, the UK's leaders in the application of the neuroscience of the electroencephalogram (EEG) to remediate trauma, trading as BrainTrainUK.

I'm writing to ask that you consider doing one small thing that can help more traumatised young people in a significant way:

Please direct the Adoption Support Fund to add EEG Neurotherapy to their list of approved interventions.

Why? Our services meet very pertinent needs:

- There is a rise in demand: 30% children in extended lockdowns display PTSD symptoms[2].
- Supply of mental health services was already limited. Many mental health interventions don't scale easily. We have a scalable model that enables local authorities and CAMHS to in-source this intervention.
- The scarcely available interventions are ineffective with many traumatised children, for two reasons:
    - Their minds don't remember the trauma (though their bodies, including their brains, do), so talking therapy/EMDR won't work;
    - Their minds do remember the trauma and they find it too overwhelming to re-visit it, so talking therapy/EMDR can't work.

  Our approach solves both these problems, as the conscious mind plays no direct part in the therapy.

  There is no need to remember, there is no need to re-imagine, there is no need to talk about what happened. If you have no memory it works just as well.

To enable assessment of efficacy, we will deliver regular summary reports of our experiences and outcomes.

I've enclosed a report[1] that explains in more detail the background, what we do, the scientific evidence behind it, and the Return on Investment (£78,000 per £5,000 intervention). The RoI has been reviewed by the Centre for Health Economics (CHE) at York University.

The Adoption Support Fund have told me that they only need your approval to be able to fund this therapy.

We'd be pleased to brief you and your team in more detail if this would be helpful before making such a decision, and would be pleased to jump through any hoops that you or ASF deem necessary.

Yours sincerely,

Stuart Black
BSc(Eng) MSc CEng MEIT
Managing Director
BrainTrainUK
stuart@braintrainuk.com
+44 7796 266 377

Refs:

[1]Black, S., & Shah, S. (2020). Developmental Trauma and Applied EEG Neuroscience - Transforming Life Outcomes with EEG Brain Mapping and EEG Neurofeedback Therapy, *Applied Neuroscience Solutions Ltd.*

[2]Sprang, G., & Silman, M. (2013). Posttraumatic stress disorder in parents and youth after health-related disasters. *Disaster medicine and public health preparedness*, *7*(1), 105-110.

Enc: Ref 1

Defence Committee
Chairman, Rt Hon Dr Julian Lewis MP
Committee Office, House of Commons, London SW1A 0AA
020 7219 6872 defcom@parliament.uk www.parliament.uk/defcom

Stuart Black BSc(Eng) MSc CEng MEIT
Managing Director
BrainTrainUK
Runnymeade Malthouse
Malthouse Lane
Egham
Surrey TW20 9BD

14 January 2019

Dear Stuart,

Thank you for your letter of 31 December about using EEG analysis to screen combat trauma victims for potential future mental health issues. I have forwarded it to the National Centre for Trauma and to Blind Veterans UK, the two organisations who gave us evidence about brain trauma and who are therefore most likely to be interested in your work.

I shall let you know what feedback we receive,

All best wishes,

Julian

BrainTrainUK
Changing Lives With Neurofeedback

Rt Hon Dr Julian Lewis MP
Chairman, House of Commons Defence Select Committee
House of Commons
Westminster
London
SW1A 0AA

31 December 2018

Dear Julian,

We noted the comments attributed to you by the Mail on Sunday 30th December 2018 regarding the availability of 7 Tesla MRI scanners to screen combat trauma victims for potential future mental health issues.

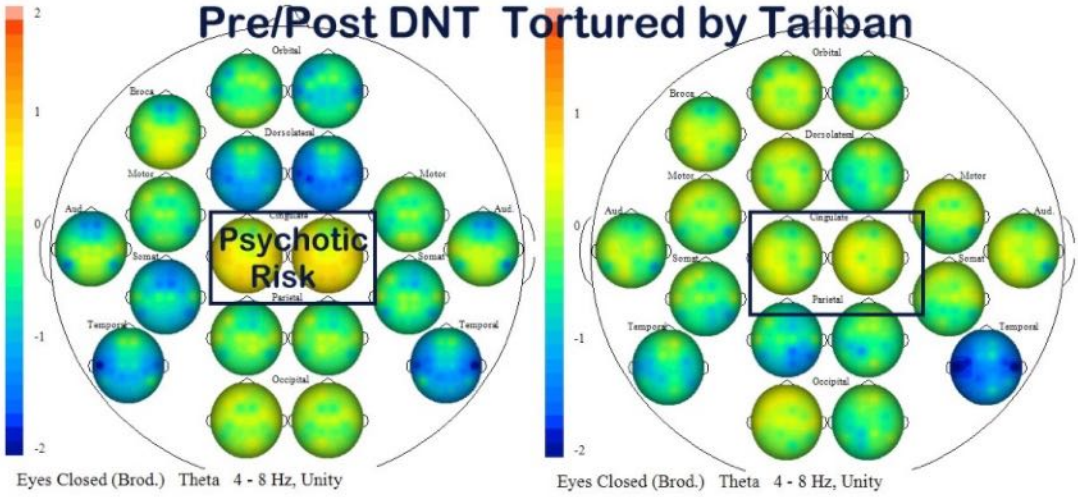
We would like to draw your attention to the potential of electroencephalogram (EEG) analysis for this purpose.

Structural imaging techniques such as MRI will identify serious structural damage. They will not easily identify the micro-tears that can occur after trauma that can cause functional damage, which if not identified and addressed can lead to serious mental health issues.

We offer an advanced analysis technique using the electrical activity (EEG) in the brain (brainwaves). We can identify functional deficiencies in brain function. We can relate these functional deficiency patterns to psychological risks through neuromarkers. Neuromarkers include post-traumatic stress disorder (PTSD) and suicidality.

EEG capture technology is well established and the equipment is portable and costs of the order of £,000s.

To bring it to life, below are 'before' and 'after' brain maps for someone tortured by the Taliban. In between they received sessions of neurofeedback therapy, designed to address the issues identified by the brain maps:



Our Advanced QEEG Brain Mapping technique has recently been adopted by Surrey County Council's Virtual School who have commissioned us to run a pilot scheme for 5 Looked After Children.

We would be pleased to brief you and/or your committee on our approach and how it might be used in-service.

Yours sincerely,

Stuart Black
BSc(Eng) MSc CEng MEIT
Managing Director
BrainTrainUK
stuart@braintrainuk.com
+44 7796 266 377

Subject: RE: Please can you route the attached letter to Brigadier Hodgetts ?
Date: Wednesday, 10 August 2016 at 18:05:42 British Summer Time
From: SG-DMed-MedD-D(Hodgetts, Timothy Brig)
To: Stuart Black
Attachments: 138E0FF1-005C-4B0D-B768-32E5144FDE06[6].png

Stuart

Received thank you. I will speak to my hearing loss expert and get back to you.

Regards

Tim

Brigadier TJ Hodgetts CBE PhD MMEd MBA
Medical Director Defence Medical Services

0121 415 8882 | @DMSMedDir

-----Original Message-----
From: Stuart Black [sblack@xcdservices.com]
Sent: Wednesday, August 10, 2016 05:20 PM GMT Standard Time
To: SG-DMed-MedD-D(Hodgetts, Timothy Brig)
Subject: Please can you route the attached letter to Brigadier Hodgetts ?

Stuart Black
XCD Consulting
Exceed the limitations of conventional thinking
sblack@xcdservices.com
07796 266 377

NEUROFLOW

BrainTrainUK
Changing Lives With Neurofeedback

10 August 2016

Brigadier Tim Hodgetts CBE
Medical Director
Defence Medical Services

Dear Brigadier Hodgetts,

We met on 9th February at the CDE Innovation Network Event at the Royal Society of Medicine.

I described two prospective proposals related to our work with the electroencephalogram (EEG) and Tinnitus, namely:

- Clinical trial of neurofeedback for treatment of tinnitus
- Long-term study of evoked response potentials to predict onset of tinnitus

You encouraged us to make these proposals and kindly pointed me in the direction of Frimley Park Hospital's Military Clinical Director to scope sourcing NHS patients for any potential studies.

Subsequently I met with Lt. Col. Nnaemeka Okpala, ENT specialist at FPH who was very supportive and we made two proposals as described above.

Neither proposal was successful in being funded as they did not meet appropriate criteria, which we accept. I felt that the feedback for the ERP-based proposal indicated some misunderstandings on the part of the assessors so resubmitted with clarification, but the resulting assessment was an even more unequivocal 'no fund'.

However, because there was real interest in the possibilities presented by our proposals and the difference they might make if further investigated, I am reluctant to give up the possibility to progressing these ideas in a different way.

I have summarised the feedback below, and attached copies of the proposals, but my real question and reason for writing is to ask **if you are in a position to offer advise on whether there might be alternative funding routes or research strategies we might pursue to advance these ideas?**

I'd be pleased to speak or meet with you to discuss this.

> Summary of feedback on PoC feasibility study for clinical trial of neurofeedback for treatment of tinnitus (CDE100713) (***our emphasis***)
>
> Fully developed, assessors considered that ***this solution may provide an approach within a clinical-setting to treating tinnitus. There is already evidence that neurofeedback already has role to play in the management of tinnitus***. ***However all the current proposal (as described in the submission) was looking to do was expand that existing evidence by conducting a larger randomised clinical trial.*** The proposal set out to use of off-the-shelf equipment in a way that was already commercially

available and whilst the study subject group was military personnel, ***this was not innovative in itself***.

Summary of feedback on PoC for long-term monitoring of evoked response potentials to predict onset of tinnitus (CDE100476) (***our emphasis***)

The question of whether evoked response potentials (ERP) precede hearing difficulties is an interesting one and something that the assessment panel agree clearly needs answering. Although the proposal was challenging in the sense of producing a good piece of work in the time proposed **the assessors didn't consider the research to be highly challenging in the scientific sense.**

Yours sincerely,

Stuart Black

Managing Director

stuart@braintrainuk.com

07796 266 377

encs:
CDE100713
CDE100476

References

[1] Black, S. Shah, S., Developmental Trauma and Applied EEG Neuroscience - Transforming Life Outcomes with EEG Brain Mapping and EEG Neurofeedback Therapy. Applied Neuroscience Solutions Ltd. 2020.

[2] Pybis, J., Saxon, D., Hill, A. et al. The comparative effectiveness and efficiency of cognitive behaviour therapy and generic counselling in the treatment of depression: evidence from the 2nd UK National Audit of psychological therapies. BMC Psychiatry 17, 215 (2017)

[3] Guessoum, Sélim Benjamin et al. "Adolescent psychiatric disorders during the COVID-19 pandemic and lockdown." Psychiatry research vol. 291 (2020): 113264. doi:10.1016/j.psychres.2020.113264

[4] Sprang, G., & Silman, M. (2013). Posttraumatic stress disorder in parents and youth after health-related disasters. Disaster medicine and public health preparedness, 7(1), 105-110.

[5] Transforming Diagnosis, Thomas Insel, National Institute for Mental Health website, 2013, retrieved from https://www.nimh.nih.gov/about/directors/thomas-insel/blog/2013/transforming-diagnosis

[6] Nuwer, Marc. "Assessment of digital EEG, quantitative EEG, and EEG brain mapping: report of the American Academy of Neurology and the American Clinical Neurophysiology Society." *Neurology* 49.1 (1997): 277-292.

[7] Rose, Todd. *The end of average: How to succeed in a world that values sameness*. Penguin UK, 2016, pp.19-22.

[8] Miller, Michael B., et al. "Extensive individual differences in brain activations associated with episodic retrieval are reliable over time." *Journal of Cognitive Neuroscience* 14.8 (2002): 1200-1214.

[9] https://nebahealth.com/products/neba-adhd-brainwave-assessment-aid/

[10] https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/denovo.cfm?ID=DEN110019

[11] Kropotov, J.D. et al. "Independent component approach to the analysis of EEG recordings at early stages of depressive disorders." *Clinical Neurophysiology*, 121.3 (2010) pp.281-289.

[12] Kropotov, Juri D. *Functional neuromarkers for psychiatry: Applications for diagnosis and treatment*. Academic Press, 2016.

[13] Ogrim, G., Kropotov, J., Brunner, J.F., Candrian, G., Sandvik, L. and Hestad, K.A., 2014. Predicting the clinical outcome of stimulant medication in pediatric attention-deficit/hyperactivity disorder: data from quantitative electroencephalography, event-related potentials, and a go/no-go test. *Neuropsychiatric disease and treatment*, *10*, p.231.

[14] Kaiser, David A. "Basic principles of quantitative EEG." *Journal of Adult Development* 12.2-3 (2005): 99-104.

[15] Sterman, M. Barry, and David Kaiser. "Comodulation: A new QEEG analysis metric for assessment of structural and functional disorders of the central nervous system." *Journal of Neurotherapy* 4.3 (2000): 73-83.

[16] Cannon, W. B. (1932). Homeostasis. *The wisdom of the body*. Norton, New York.

[17] Brown, B. (1974). *New Mind, New Body Bio-Feedback: New Directions for the Mind*. Harper & Row, 10.

[18] Van Der Kolk, B. (2015). The body keeps the score: Brain, mind, and body in the healing of trauma. Penguin Books.

[19] PracticeWise Blue Menu of Evidece Based PsychoSocial Interventions for Youth, https://www.practicewise.com/portals/0/forms/PracticeWise_Blue_Menu_of_Evidence-Based_Interventions.pdf , retrieved 20/12/16.

[20] Gruzelier, J. H. (2014). EEG-neurofeedback for optimising performance. I: a review of cognitive and affective outcome in healthy participants. *Neuroscience & Biobehavioral Reviews*, 44, 124-141.

[21] Peniston, E. G., & Kulkosky, P. J. (1989). α-θ Brainwave Training and β-Endorphin Levels in Alcoholics. *Alcoholism: Clinical and experimental research*, *13*(2), 271-279.

[22] Peniston, E. G., & Kulkosky, P. J. (1991). Alpha-theta brainwave neurofeedback for Vietnam veterans with combat-related post-traumatic stress disorder. *Medical Psychotherapy*, *4*(1), 47-60.

[23] Scott, W. C., Kaiser, D., Othmer, S., & Sideroff, S. I. (2005). Effects of an EEG biofeedback protocol on a mixed substance abusing population. *The American journal of drug and alcohol abuse*, *31*(3), 455-469.

[24] van der Kolk, Bessel A., et al. "A randomized controlled study of neurofeedback for chronic PTSD." *PloS one* 11.12 (2016): e0166752.

[25] Panisch, Lisa S., and Audrey Hang Hai. "The effectiveness of using neurofeedback in the treatment of post-traumatic stress disorder: a systematic review." *Trauma, Violence, & Abuse* (2018): 1524838018781103.

[26] Ghaziri, Jimmy, et al. "Neurofeedback training induces changes in white and gray matter." *Clinical EEG and neuroscience* 44.4 (2013): 265-272.

[27] Harvey, Alison, et al. "The future of technologies for personalised medicine." *New biotechnology* 29.6 (2012): 625-633.

[28] Ros T, Theberge J, Frewen PA, et al: Mind over chatter: Plastic up- regulation of the fMRI salience network directly after EEG neuro- feedback. *Neuroimage* 65:324-335, 2013

[29] Zhang G, Zhang H, Li X, et al: Functional alteration of the DMN by learned regulation of the PCC using real-time fMRI. *IEEE Trans Neural Syst Rehabil Eng* 21:595-606, 2013

[30] Cincotti, F., Kauhanen, L., Aloise, F., Palomäki, T., Caporusso, N., Jylänki, P., ... & Marciani, M. G. (2007). Vibrotactile feedback for brain-computer interface operation. Computational intelligence and neuroscience, 2007.

[31] Othmer, S., Othmer, S. F., Kaiser, D. A., & Putman, J. (2013, December). Endogenous neuromodulation at infralow frequencies. *Seminars in pediatric neurology* (Vol. 20, No. 4, pp. 246-257). WB Saunders.

[32] https://www.nice.org.uk/about/who-we-are/our-charter

[33] https://www.nice.org.uk/guidance/ng116/documents/committee-member-list

[34] Telephone call S Black – A Pike 13th April 2021

[35] Post-traumatic stress disorder (PTSD) (update) Committee meeting 6 Date: 18th July 2017

[36] Juma, C. (2016). *Innovation and its enemies: Why people resist new technologies*. Oxford University Press.

[37] Wood, Lesley, et al. "Empirical evidence of bias in treatment effect estimates in controlled trials with different interventions and outcomes: meta-epidemiological study." *Bmj* 336.7644 (2008): 601-605.

[38] Higgins, J. P., Altman, D. G., Gøtzsche, P. C., Jüni, P., Moher, D., Oxman, A. D., ... & Sterne, J. A. (2011). The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *Bmj*, *343*.

[39] Attention deficit hyperactivity disorder (update) [E] Evidence review(s) for efficacy of nonpharmacological treatment and the impact of adverse events associated with nonpharmacological treatments of ADHD, March 2018, p120, retrieved March 2021 https://www.nice.org.uk/guidance/ng87/evidence/e-nonpharmacological-efficacy-and-adverse-events-pdf-4783686305

[40] NICE Post-traumatic stress disorder [D] Evidence reviews for psychological, psychosocial and other non-pharmacological interventions for the treatment of PTSD in adults, 2018, p367, retrieved March 2021 https://www.nice.org.uk/guidance/ng116/evidence/d-psychological-psychosocial-and-other-nonpharmacological-interventions-for-the-treatment-of-ptsd-in-adults-pdf-6602621008

[41] Bellis, Mark A., et al. "Measuring mortality and the burden of adult disease associated with adverse childhood experiences in England: a national survey." *Journal of public health* 37.3 (2014): 445-454.

[42] Chowdry, Haroon, and Peter Fitzsimons. *The cost of late intervention: EIF analysis 2016*. London: Early Intervention Foundation, 2016.

[43] Evidence reviews for psychological, psychosocial and other non-pharmacological interventions for the treatment of PTSD in adults, *NICE guideline NG116 Evidence reviews*, December 2018.

[44] Mihalopoulos, Cathrine, et al. "Is implementation of the 2013 Australian treatment guidelines for posttraumatic stress disorder cost-effective compared to current practice? A cost-utility analysis using QALYs and DALYs." *Australian & New Zealand Journal of Psychiatry* 49.4 (2015): 360-376.

[45] Haagsma, Juanita A., et al. "Posttraumatic stress symptoms and health-related quality of life: a two year follow up study of injury treated at the emergency department." *BMC psychiatry* 12.1 (2012): 1-8.

[46] Evidence reviews for psychological, psychosocial and other non-pharmacological interventions for the treatment of PTSD in adults, *NICE guideline NG116 Evidence reviews*, December 2018, p.1113

[47] NICE (2013) Guide to the methods of technology appraisal 2013 (PMG9)

[48] O'Mahony, J. F., & Paulden, M. (2014). NICE's selective application of differential discounting: ambiguous, inconsistent, and unjustified. Value in Health, 17(5), 493-496.

[49] NICE (2020) The NICE methods of health technology evaluation: the case for change Appendix 1 para 14.

[50] Evidence reviews for psychological, psychosocial and other non-pharmacological interventions for the treatment of PTSD in adults, *NICE guideline NG116 Evidence reviews*, December 2018, p.1120, Table 202 Annual health and personal social service costs incurred by adults with PTSD and adults without PTSD

[51] Private email correspondence with Dr Mathew Taylor, Director York Centre for Health Economics.

[52] Chapman, C., et al. "Remission from post-traumatic stress disorder in the general population." *Psychological medicine* 42.8 (2012): 1695.

[53] Edlin, Richard, et al. *Cost effectiveness modelling for health technology assessment: a practical course*. Springer, 2015.

[54] Goldway, N., Ablin, J., Lubin, O., Zamir, Y., Keynan, J.N., Or-Borichev, A., Cavazza, M., Charles, F., Intrator, N., Brill, S. and Ben-Simon, E. (2018). Volitional limbic neuromodulation has a multifaceted clinical benefit in Fibromyalgia patients. *Neuroimage*, *186*, pp.758-770.

[55] Wyrwicka, W, & Sterman, M. B. (1968). Instrumental conditioning of sensorimotor cortex EEG spindles in the waking cat. *Physiology and Behavior*, 3, 703-707.

[56] Sterman, M. B., LoPresti, R. W., & Fairchild, M. D. (1969). Electroencephalographic and behavioral studies of monomethylhydrazine toxicity in the cat. CALIFORNIA UNIV LOS ANGELES BRAIN RESEARCH INST.

[57] Sterman, M. B. (2000). Basic concepts and clinical findings in the treatment of seizure disorders with EEG operant conditioning. *Clinical EEG and Neuroscience*, 31(1), 45-55.

[58] Hagemann, D., Hewig, J., Seifert, J., Naumann, E., & Bartussek, D. (2005). The latent state trait structure of resting EEG asymmetry: Replication and extension. Psychophysiology, 42(6), 740-752.

[59] Wood, J. D., & Peesker, S. J. (1974). Development of an expression which relates the excitable state of the brain to the level of GAD activity and GABA content, with particular reference to the action of hydrazine and its derivatives. *Journal of neurochemistry*, 23(4), 703-712.

[60] Sterman, M. B. (1996). Physiological origins and functional correlates of EEG rhythmic activities: implications for self-regulation. *Biofeedback and self-regulation*, 21(1), 3-33.

[61] https://bestpractice.bmj.com/info/toolkit/learn-ebm/what-is-grade/

[62] Mustafa, R. A., Santesso, N., Brozek, J., Akl, E. A., Walter, S. D., Norman, G., ... & Schünemann, H. J. (2013). The GRADE approach is reproducible in assessing the quality of evidence of quantitative evidence syntheses. *Journal of clinical epidemiology*, *66*(7), 736-742.

[63] Higgins, Julian PT, et al. "The Cochrane Collaboration's tool for assessing risk of bias in randomised trials." *Bmj* 343 (2011).

[64] Guyatt, Gordon H., et al. "GRADE guidelines 6. Rating the quality of evidence—imprecision." *Journal of clinical epidemiology* 64.12 (2011): 1283-1293.

[65] Guyatt, Gordon H., et al. "GRADE guidelines: 7. Rating the quality of evidence—inconsistency." *Journal of clinical epidemiology* 64.12 (2011): 1294-1302, Fig 3.

[66] Guyatt, Gordon H., et al. "GRADE guidelines: 8. Rating the quality of evidence—indirectness." *Journal of clinical epidemiology* 64.12 (2011): 1303-1310.

[67] Guyatt, Gordon H., et al. "GRADE guidelines: 9. Rating up the quality of evidence." *Journal of clinical epidemiology* 64.12 (2011): 1311-1316.