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EEG-based neurofeedback as treatment for post-traumatic stress disorder

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VÄSTRA GÖTALANDSREGIONEN
SAHLGRENSKA UNIVERSITETSSJUKHUSET

EEG-based neurofeedback as treatment for post-traumatic stress disorder

[EEG-baserad neurofeedback som behandling för post-traumatiskt stressyndrom]

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1. Abstract

Background
Posttraumatic stress disorder (PTSD) has been defined as the development of characteristic symptoms following exposure to extreme traumatic stressor(s), including persistently re-experiencing the trauma affecting cognition and mood negatively. Posttraumatic stress disorder is associated with problems in maintaining an employment and establishing social relations, as well as increased need for disability support. Present national and regional guidelines for PTSD recommend psychoeducation, psychotherapy, treatment for insomnia, and pharmacotherapy. Neurofeedback is not a part of current recommendations. EEG-based neurofeedback is a non-invasive method for reestablishing the electrophysiological activity of the brain, thus reducing symptoms related to over- or understimulation of different parts of the brain.

Objectives
The objective of this Health Technology Assessment (HTA) was to assess whether EEG-based neurofeedback is an effective treatment for patients with PTSD compared with sham neurofeedback, other treatment or no treatment. Measures of self-harm and suicidal thoughts, PTSD symptoms, level of functioning, and health-related quality of life were considered critical outcomes for decision-making. The degree of sick leave, medication use, complications and patients' experience of the treatment were considered important outcomes.

Methods
A systematic literature search was conducted in November 2018 in PubMed, Embase, the Cochrane Library, Cinahl, PsycINFO, Web of Science, and a number of HTA databases. The certainty of evidence was assessed using the GRADE approach.

Main results
No study was identified that evaluated neurofeedback treatment versus sham neurofeedback. Four small RCTs were identified, including 12 to 52 participants each that examined the effects of EEG-based neurofeedback in patients with PTSD. All studies reported outcomes immediately after treatment and follow-up data were collected in two studies. Three studies compared EEG-based neurofeedback with no treatment. The fourth study compared EEG-based neurofeedback with standard treatment. Suicidal thoughts were investigated in one study and were reported to be significantly reduced more after neurofeedback treatment compared with controls who were on waiting list. PTSD symptoms were assessed with different instruments in all studies post-treatment (in one study also at 1 month follow-up) and results were consistently in favour of neurofeedback with large effect sizes (standardized mean difference -2.30 (95% CI -4.37 to -0.24). One study reported significantly improved level of functioning (cognitive performance tests) after neurofeedback. In one study reduction of medication use was achieved in significantly more patients in the neurofeedback group than in the standard treatment group (14/14 vs 1/13). Complications were only sparsely reported. None of the studies evaluated effects of neurofeedback treatment on health-related quality of life, sick leave, or patient experience of the treatment.

Concluding remarks
No study evaluated EEG-based neurofeedback versus sham neurofeedback, and hence a placebo effect cannot be excluded. Based on three small RCTs, with several study limitations and imprecision, it is uncertain whether EEG-based neurofeedback compared with no treatment or standard treatment reduces PTSD symptoms post-treatment in adult patients with PTSD (very low certainty of evidence, GRADE ⊕◯◯◯). It is also uncertain whether EEG-based neurofeedback treatment results in any difference in suicidal thoughts, level of functioning, or medication use compared with no or other treatment (very low certainty of evidence, GRADE ⊕◯◯◯). Health-related quality of life, sick leave, and patients' experience of treatment were not studied in the RCTs, and information on complications was sparse. Equipment costs and training needs for implementation of EEG-based neurofeedback are modest.

If it is introduced as additional treatment after failure of currently offered treatment options, additional personnel, treatment rooms, and equipment may be needed. Given the need for treatment options for PTSD, further research on the use of EEG-based neurofeedback for this population is motivated.

2. Svensk sammanfattning – Swedish summary

Bakgrund
Posttraumatisk stressyndrom (PTSD) definieras som utveckling av karakteristiska symptom efter upplevelse av traumatisk stress. Symptomen innefattar återkommande återupplevelser av traumat vilket påverkar kognition och stämningsläge negativt. Tillståndet medför ofta problem i sociala relationer, svårigheter att behålla sitt arbete, och behov av sjukskrivning. Aktuella nationella och regionala riktlinjer för behandling av PTSD rekommenderar psykoedukation, psykoterapi, läkemedelsbehandling, och behandling för sömnsvårigheter. Neurofeedback finns inte med i de aktuella riktlinjerna. EEG-baserad neurofeedback är en icke-invasiv metod för att återupprätta hjärnans elektrofysiologiska aktivitetsnivå. Målsättningen med neurofeedback är att minska symptom som är relaterade till över- eller understimulering av olika delar av hjärnan.

Syfte
Syftet med denna HTA-rapport var att utvärdera om EEG-baserad neurofeedback är en effektiv behandlings-metod för patienter med PTSD jämfört med simulerad neurofeedback, annan behandling eller ingen behandling. Kritiska utfallsvariabler i analysen var självskadebeteende och suicidtankar, PTSD-symptom, funktions-förmåga, och hälsorelaterad livskvalitet. Viktiga utfallsvariabler var läkemedelsförbrukning, sjukskrivning, komplikationer, och patientens upplevelse av behandlingen.

Metod
En systematisk litteratursökning genomfördes i november 2018 i PubMed, Embase, Cochrane Library, Cinahl, PsycINFO, Web of Science, och ett antal HTA-databaser. Studiernas kvalitet utvärderades och GRADE-systemet användes för att bedöma tillförlitligheten hos de sammanvägda resultaten.

Resultat
Ingen studie identifierades som har jämfört neurofeedback med simulerad neurofeedback. Fyra mindre randomiserade kontrollerade studier identifierades som undersökte behandling med EEG-baserad neurofeedback av patienter med PTSD (12 till 52 patienter per studie). Alla studier rapporterade utfallen direkt vid behandlingsslut och två studier rapporterade även en uppföljning av patienterna efter avslutad behandling. Tre studier jämförde neurofeedback med ingen behandling. Den fjärde studien jämförde EEG-baserad neurofeedback med standardbehandling. En studie visade att deltagarnas suicidtankar minskade signifikant mer efter behandling med neurofeedback jämfört med ingen behandling. I alla studier undersöktes PTSD-symptom med olika mätmetoder efter behandlingen (i en studie även 1 månad efter behandlingsslut) och resultaten visade genomgående en fördel för neurofeedback med stor effektstorlek (standardiserad medelvärdesskillnad -2,3, 95 % konfidensintervall -4,37 till -0,24). I en studie observerades signifikant förbättrad kognitiv funktionsnivå efter neurofeedback jämfört med ingen behandling. En studie rapporterade minskning av läkemedelsanvändning hos signifikant fler patienter (14/14) efter neurofeedback än efter standardbehandling (1/13). Komplikationer utvärderades sparsamt. Ingen studie undersökte effekt på hälsorelaterad livskvalitet, sjukskrivning eller patienters upplevelse av behandlingen.

Sammanfattande kommentarer
Ingen studie utvärderade neurofeedback jämfört med simulerad neurofeedback, vilket innebär att eventuella placeboeffekter inte kan uteslutas. Baserat på fyra små studier med olika begränsningar avseende studiekvalitet och precision är det osäkert huruvida EEG-baserad neurofeedback har effekt på

PTSD-symptom vid behandlingsslut hos vuxna patienter med PTSD jämfört med ingen behandling eller standardbehandling (mycket låg tillförlitlighet, GRADE ⊕◯◯◯). Det är även osäkert huruvida EEG-baserad neurofeedback har effekt på suicidtankar, funktionsnivå, och läkemedelsanvändning (mycket låg tillförlitlighet, GRADE ⊕◯◯◯). Hälsorelaterad livskvalitet, sjukskrivning, och patientens upplevelse av behandlingen har inte undersökts i de fyra studierna och informationen om komplikationer var mycket begränsad. Kostnader för utrustning och utbildning för att implementera EEG-baserad neurofeedback är blygsamma. Om metoden införs som ytterligare behandling i de fall nuvarande behandlingsalternativ inte har gett resultat kan dock ytterligare kostnader tillkomma för mer personal, behandlingsrum och utrustning. Då det behövs behandlingsalternativ för PTSD är mer forskning på EEG-baserad neurofeedback för denna patientgrupp motiverat.

The above summaries were written by representatives from the HTA-centrum. The HTA report was approved by the Regional board for quality assurance of activity-based HTA. The abstract is a concise summary of the results of the report. The Swedish summary is a brief summary of the report intended for decision makers.

Christina Bergh, Professor, MD
Head of HTA-centrum of Region Västra Götaland, Sweden, 15 April, 2019

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Svensson, Mikael	Health economist, Professor
Wallerstedt, Susanna	MD, Professor
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DDS Doctor of Dental Surgery
MD Medical Doctor
PhD Doctor of Philosophy
OD Odontology Doctor
RPT Registered Physiotherapist
RN Registered Nurse

3. Summary of findings

Outcome	Number and type of studies (participants)	Absolute effect estimates	Certainty of evidence GRADE[1]
EEG-based neurofeedback vs sham neurofeedback			
This comparison was not evaluated in any of the included studies.			
EEG-based neurofeedback vs other treatment			
PTSD symptoms	1 RCT (n=29)	Between-group difference in mean change pre-to-post treatment: Δ 20.4 in favour of neurofeedback (scale 0-49), p<0.05	⊕○○○[2]
Medication use	1 RCT (n=29)	Number of patients with decreased medication use Decrease: 14/14 vs 1/13 Between-group difference: χ^2= 23.26, p<0.05	⊕○○○[2]
EEG-based neurofeedback vs no treatment			
Suicidal thoughts	1 RCT (n=10)	Between-group difference in mean change pre-to-post treatment: Δ 1.4 in favour of neurofeedback (scale 1-5), p=0.002	⊕○○○[3]
PTSD symptoms	3 RCTs (n=92)	Standardised mean difference -2.30 (95% CI -4.27 to -0.24), p=0.03	⊕○○○[4]
Level of functioning	1 RCT (n=30)	Wisconsin Card Sorting Test No. of errors: Between-group difference in mean change pre-to-post treatment: Δ 29.4 in favour of neurofeedback, p<0.001 Tower of London Between-group difference in mean change pre-to-post treatment: Δ 6.1 in favour of neurofeedback, p<0.001	⊕○○○[5]

[1]Certainty of evidence

High certainty ⊕⊕⊕⊕	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty ⊕⊕⊕○	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty ⊕⊕○○	Confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low certainty ⊕○○○	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[2]Downgraded three steps for serious study limitations, indirectness and serious imprecision (e.g. unclear randomisation, lack of blinding, unclear whether data analyses were pre-defined, different preconditions in control treatment, one small study)
[3]Downgraded three steps for very serious study limitations, indirectness, and serious imprecision (e.g. self-reported outcomes with no blinding, unclear whether data analyses were pre-defined, different preconditions in control treatment, one very small study)
[4]Downgraded three steps for very serious study limitations and serious imprecision (e.g. different preconditions in control treatment, limitations in blinding, questions whether data analyses were pre-defined, heterogeneity)
[5]Downgraded three steps for very serious study limitations and serious imprecision (e.g. different preconditions in control treatment, unclear randomisation, lack of blinding, questions whether data analyses were pre-defined)

Abbreviations/Acronyms

CAPS = Clinician-administered PTSD scale
CBT = Cognitive behavioural therapy
CI = Confidence interval
CTU = Crisis and Trauma Unit
DSM = Diagnostic and statistical manual of the American Psychiatric Association
DTS = Davidson trauma scale
EEG = Electroencephalography
EMDR = Eye movement desensitisation and reprocessing
IES-R = Impact of event scale-revised
ILF = Infra low frequency
MMPI = Minnesota multiphasic personality inventory
PMG = Psykiatrimottagning Gamlestaden (Psychiatric clinic Gamlestaden)
PTSD = Post-traumatic stress disorder
SBU = Statens beredning för medicinsk och social utvärdering
SMD = Standardised mean difference
SSRI = Selective serotonin re-uptake inhibitors
TOL = Tower of London
VGR = Region Västra Götaland
WHO = World Health Organization
WCST = Wisconsin card sorting test

4. Background

Disease/disorder of interest and its degree of severity

Posttraumatic stress disorders (PTSD) has been defined by the Diagnostic and Statistical Manual of the American Psychiatric Association (DSM-5) as the development of characteristic symptoms following exposure to extreme traumatic stressor(s), including persistently re-experiencing the trauma leading to negative changes in cognition and mood, and avoidance behaviour (American Psychiatric Association, 2013). The DSM-5 definition includes a time frame of at least one month with clinically significant distress or impairment in social, occupational, or other important areas of functioning. Another way of summarising PTSD is to describe it as a composite of "somatic, cognitive, affective, and behavioural effects of psychological trauma" (van der Kolk et al., 1996) that often leads to problems in maintaining an occupation, establishing social support, and increased rate of disability support (Solomon & Davidson, 1997). There are numerous different traumas that can lead to PTSD and there is a number of physical consequences associated with the diagnosis. Common PTSD symptoms include re-experiencing of trauma, sleep disturbance, irritability and guilt feelings.

A three year follow up study on European refugees after the war in Bosnia and Herzegovina, showed that occurrence of medical conditions, such as high blood pressure (38%) and heart disease (31%), were frequent among those diagnosed with PTSD and depression (Vukovic et al., 2014). As a reference, global prevalence of raised blood pressure has been reported as 24% in men and 20% in women (NCD Risk Factor Collaboration, 2017). Furthermore, a population-based study showed increased risk for angina, heart failure, bronchitis, asthma, liver, and peripheral arterial disease (odds ratio range between 2.4 and 3.4) for those with a history of trauma compared with a general population, adjusted for sociodemographic factors, smoking, body mass index, blood pressure, depression, and alcohol use disorder (Spitzer at al., 2009). A more immediate threat to life is the increased risk for suicide in patients with PTSD compared with the general population. This risk was estimated to be around 10 times higher in a registry study in Denmark, and when adjusted for other psychiatric co-morbidities the risk was still 5.3 times higher for patients with PTSD (Gradus et al., 2010).

Prevalence and incidence of PTSD

The average prevalence of PTSD in upper-middle income and lower-middle income countries is 2.3% and 2.1%, respectively, according to the World Health Organization (Koenen et al., 2017). In national samples of the general adult population in the United States and Canada, lifetime prevalence is reported to be between 6.1% and 9.2% (Kessler et al., 2005; Goldstein et al., 2016; van Ameringen et al., 2008). In Sweden, the prevalence of PTSD has been estimated to be 5.6% in a population-based study, with a sex ratio of one man for every two women (Frans et al., 2005). The differing rates may be related to the method of obtaining the rate.

A particular problem in diagnosing PTSD may be the overlap of symptoms with other psychiatric disorders. The National Comorbidity Survey data, a large survey of mental health in the United States of America, suggests that 16% of PTSD patients have one coexisting psychiatric disorder, 17% two and 50% have three or more (Kessler et al., 1995). Most common comorbidities are depressive disorder, anxiety disorder, and substance abuse.

Present treatment for PTSD

Today, healthcare providers around the world offer a noteworthy breadth of treatment methods for PTSD, most of which are based on evidence from intervention studies (for meta-analyses, see Cramer et al., 2018; Lewis et al., 2018; Gerger, Munder & Barth, 2014; Watts et al., 2013; Benish, Imel & Wampold, 2008). In short, the best way to summarise present treatment of PTSD is that it varies considerably.

The most widely accepted methods, however, are psychotherapy (e.g. cognitive behavioural therapy (CBT), exposure therapy, eye movement desensitisation and reprocessing (EMDR)), and pharmacotherapy (especially selective serotonin re-uptake inhibitors (SSRIs)) as well as a combination of these treatments.

Moreover, social support and PTSD-adjusted physiotherapy are standard options in several countries – as complements or treatments in their own right. Across all the mentioned alternatives, treatment lengths range from two to three months to several years. Specific treatments, with a rationale manual, often apply a 20-40 session model (approximately 20-40 weeks). Typically, open treatments (i.e. without manual) apply a longer time span than that.

The normal pathway through the healthcare system and current wait time for medical assessment/treatment

In Region Västra Götaland (VGR), the normal pathway for a patient with PTSD through the healthcare system is the following: (1) the patient visits a general practitioner at the primary health care level, (2) the physician makes a screening and initiates first-line treatment, (3) if this first line treatment fails the physician contacts a specialised PTSD unit, and (4) the patient undergoes a new assessment at that unit for more specialised care. Patients may also initiate a self-referral to the tertiary care system on their own initiative.

As of today, there are four units in VGR that are specialised in the treatment of PTSD: Psykiatrisk Mottagning Gamlestaden (PMG), an outpatient clinic at the Sahlgrenska University Hospital; Crisis and Trauma Unit (CTU), Flyktingmedicinsk Mottagning (FM), and the treatment center of the Red Cross. The units differ in focus on trauma types related to PTSD: PMG focuses on crisis reactions in general whereas CTU, FM and the Red Cross focus on war, torture and refugee-related trauma. Waiting time for assessment from time of referral (including self-referral) varies between immediate (acute situations, FM) to approximately one month. However, actual time to initiation of treatment is longer, approximately 1-3 months.

Number of patients per year who undergo current treatment regimen

At Sahlgrenska University Hospital's PMG, a total of 290 patients were under treatment or active follow-up in December 2018. In total, 62% were women, 23% were in need of interpreter, one of three were currently in employment or studying, while 40% were on sick leave and 22% had permanent disability pension. During a single year (2017), 9% of these 290 patients visited the clinic's psychiatric emergency room and 6% were admitted to the inpatient ward.

Present recommendations from medical societies or health authorities

In Sweden, national guidelines for PTSD from the National Board of Health and Welfare (Socialstyrelsen, 2017) state that public health care *should* offer trauma-focused CBT with exposure, and *may* offer EMDR and antidepressants. Importantly, the guidelines also underscore that the state of research on PTSD treatments is insufficient, and that more studies are needed to draw clear-cut conclusions.

For PTSD the VGR regional guidelines (Västra Götalandsregionen, 2016) recommend:

- Psychoeducation and general recommendations, e.g. sleep hygiene.
- Trauma-focused psychotherapy, especially EMDR and CBT.
- Anxiety- and stress management as add-on treatment for insomnia (preferably in group sessions).
- Pharmacotherapy if psychotherapy is not possible, with SSRIs, non-addictive anxiolytics or beta-blockers.

Integrated methods are recommended in case of co-morbid substance use disorder. Neurofeedback is currently not mentioned in the Swedish guidelines on treatment of PTSD.

5. Neurofeedback

Neurofeedback is a non-invasive treatment method to reestablishing the electrophysiological activity of the brain. The aim is to reduce symptoms related to over- or understimulation within different parts of the brain. The development of neurofeedback can be traced back to the 1960s when electroencephalography (EEG) patterns were associated with behaviour. In the 1970s neurofeedback was tested among patients with Attention Deficit Hyperactivity Disorder (ADHD) and epilepsy (Othmer, 2015).

Neurofeedback treatment can be delivered in several ways, of which the two most common are EEG and functional magnetic resonance imaging (fMRI). This HTA report focuses only on EEG-based neurofeedback, in which EEG readings are used to give feedback to the individual in order to utilise neuronal plasticity to change frequency and amplitude of the neural electrical activity. The EEG-registered pattern has a direct association with activity in the underlying region. Generally, activity in the low range of frequency (delta-wave, <4 Hz) is dominant during regular sleep while medium low frequency (alpha-waves, ~10 Hz) occurs during relaxed wake. Higher frequency (beta-waves, 13-39 Hz) occurs during concentrated state. In between the alpha- and delta-wave frequency (4-7 Hz), there are theta-waves. When major parts of the brain are active on this frequency, the person finds himself in a hypnagogic state, in between being awake and asleep. This state often occurs when we are about to fall asleep and creates an opportunity for the brain to process impressions, memories and thoughts without interference from the intellectual awareness (Othmer, 2017).

Patients who suffer from PTSD are affected by flashbacks of traumatic memories, anxiety in relation to intense activity in the limbic system (hyperarousal), and symptoms of depression and cognitive impairment in relation to decreased activity in the frontal lobes (hypoarousal). When PTSD is treated with neurofeedback, the aim is to increase alpha activity in the brain through sensory feedback (e.g. visual or auditory) to increase relaxation and decrease anxiety. This is usually followed by feedback during theta activity to process traumatic memories (Othmer, 2017). Another option is to provide feedback in relation to beta activity to reduce hypoarousal. A relatively recently developed protocol of neurofeedback is called Infra Low Frequency (ILF). This treatment protocol focuses on stimulation of very low frequencies in groups of cells in the brain that surround the neurons.

Regardless of which protocol is used, the therapist applies three to five electrodes on the scalp of the patient. A computer continuously analyses the EEG of the patient. During visual feedback, the patient watches a film, images or plays a videogame on a computer screen. The computer adjusts the picture or sound, depending on the characteristics of the EEG. Thus the patient's brain receives feedback and will adjust its electrophysiological activity in order to obtain the desired quality of picture or sound (depending on feedback modality) in a continuous feedback loop. The principles are illustrated in Figure 1.

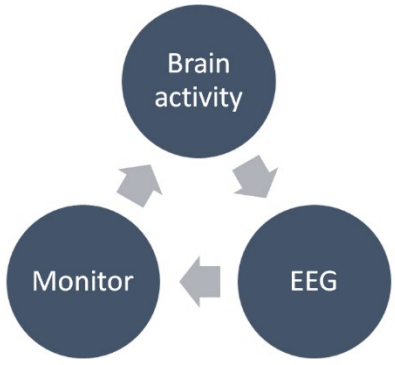

Figure 1. Feedback loop between a person's brain activity measured by EEG, which regulates in turn the output on a monitor. An example would be a picture on the monitor that gets blurry, which changes the brain activity. The EEG registers this change and adjusts the picture on the monitor.

Sometimes neurofeedback is combined with other biofeedback methods, for instance measurement of the temperature in fingers which is related to the person's ability to relax. After a few sessions the patient usually learns how to react to achieve the desired effect, and typically 20-40 sessions are suggested to obtain a lasting effect.

6. Focused question

Is EEG-based neurofeedback as treatment for patients with post-traumatic stress disorder effective on self harm, PTSD symptoms, level of functioning and health-related quality of life compared with sham neurofeedback, other treatment, or no treatment?

PICO: P= Patients, I= Intervention, C= Comparison, O=Outcome

P: Adult (≥18 years) patients diagnosed with PTSD

I: EEG biofeedback/neurofeedback (alone or in combination with other treatment)

C1: Sham neurofeedback (i.e. simulated)
C2: Other treatment (e.g. psychotherapy, medication, physiotherapy, eye movement desensitisation and reprocessing (EMDR))
C3: No treatment

O: Critical for decision making

- Self harm, including suicidality (both self-reported and observed behaviour, e.g. hospital visits) and suicidal thoughts
- PTSD symptoms measured with validated instruments
- Level of functioning measured with validated instruments
- Health-related quality of life measured with validated instruments

Important for decision making

- Sick leave/work ability
- Medication use
- Patient's own experiences of the treatment
- Complications

7. Methods

Systematic literature search (Appendix 1)

During November 2018 two authors (IS, ACE) performed systematic searches in PubMed, Embase, the Cochrane Library, Cinahl, PsycINFO, Web of Science, and a number of HTA databases. Reference lists of relevant articles were also scrutinised for additional references. Search strategies, eligibility criteria and a graphic presentation of the selection process are presented in Appendix 1. These authors conducted the literature searches, selected studies, and independently of one another assessed the obtained abstracts and made a first selection of full-text articles for inclusion or exclusion. Any disagreements were resolved in consensus. The remaining articles were sent to all authors. All authors read the articles independently of one another and it was finally decided in a consensus meeting which articles should be included in the assessment. Excluded studies and reasons for exclusion are presented in Appendix 3.

Critical appraisal and certainty of evidence

The included studies have been critically appraised using a checklist from the Swedish Agency for HTA and assessment of social services (SBU) for assessment of randomised controlled trials. The results of each study have been summarised per outcome in Appendix 4. When possible, data have been pooled for meta-analysis in RevMan 5.3 using a random effects model. Summary results per outcome and the associated certainty of evidence are presented in a Summary-of-findings table (page 7). Certainty of evidence for each outcome was assessed using the GRADE approach (Atkins et al., 2004; GRADE Work group).

Patient involvement

The PICO was reviewed by a patient with PTSD currently undergoing treatment at one of the PTSD units in Region Västra Götaland, who confirmed that the outcomes at issue and their priority were relevant.

Ongoing research

A search in Clinicaltrials.gov was performed on 17 January 2019 and identified 17 trials. The following search terms were used: (neurofeedback OR neuro-feedback OR ((brainwave OR alpha OR electromyography OR electromyographic OR EEG OR electroencephalography OR electroencephalographic)) AND (biofeedback* OR feedback* OR bio-feedback*)) AND (ptsd OR ((post-traumatic OR posttraumatic) AND (stress OR neuroses OR neurosis OR disorder*))).

8. Results

Search results

The literature search identified 219 records after removal of duplicates. After reading the abstracts, 188 articles were excluded. Another 17 articles were excluded by two authors in consensus after reading the articles in full text. The remaining 14 articles were sent to all authors, and four publications, reporting four RCTs, were finally included in the HTA report. A flowchart of the study selection process is presented in Appendix 1.

Included studies

Four randomised controlled studies that met the inclusion criteria were identified and included in the report. All studies were small (n=10-52) and were assessed as having moderate to high risk of bias, some indirectness and imprecision. Problems in the included studies were identified with confounding factors, self-reported outcomes with no blinding, and lack of published protocols. The included studies, their design, and patient characteristics are presented in Appendix 2.

Results per comparison and outcome

1. EEG-based neurofeedback vs sham neurofeedback

No studies were identified in which this comparison was investigated. One trial, identified in our search for ongoing trials, was designed to compare neurofeedback with sham-neurofeedback (ClinicalTrials.gov identifier: NCT01591408). This trial was completed in 2016, but no publication of the study could be retrieved.

2. EEG-based neurofeedback vs other treatment

Only two of the outcomes of interest, PTSD symptoms and medication use, were reported for this comparison.

PTSD symptoms (Appendix 4.2)

One RCT (Peniston, 1993), with serious study limitations, indirectness and imprecision, reported symptom reduction measured with the Minnesota Multiphasic Personality Inventory (MMPI) PTSD scale. Symptom data were collected at baseline, end of treatment and 30 months after treatment. The intervention group showed a larger reduction in symptoms post-treatment (between-group difference in change: 20.4 points, $p<0.05$). At 30 months' follow-up, relapse was reported in significantly fewer patients in the intervention group (3/15) than in the control group (14/14) ($p<0.05$).

Conclusion: It is uncertain whether EEG-based neurofeedback compared with other treatment reduces PTSD symptoms in adult patients with PTSD (very low certainty of evidence, GRADE ⊕○○○).

Medication use (Appendix 4.4)

One RCT (Peniston, 1993) reported medication use after the study period and found that in the neurofeedback group all patients (14/14) had reduced medication use according to a pre-specified protocol as compared with 1/13 in the control group ($p<0.05$).

Conclusion: It is uncertain whether EEG-based neurofeedback compared with other treatment reduces medication use in adult patients with PTSD (very low certainty of evidence, GRADE ⊕○○○).

3. EEG-based neurofeedback vs no treatment

Outcomes, critical for decision-making

Self harm, including suicidality and suicidal thoughts (Appendix 4.1)
One very small, unpublished RCT (Kelson, 2013), with serious study limitations, indirectness and imprecision, compared neurofeedback with a waiting list and reported self-rated suicidality based on one question on a scale from 1-5. The difference in mean pre- to post-treatment change was 1.4 in favour of neurofeedback (p=0.002).

Conclusion: It is uncertain whether EEG-based neurofeedback compared with waiting list reduces occurrence of suicidal thoughts in adult patients with PTSD (very low certainty of evidence, GRADE ⊕○○○).

PTSD symptoms (Appendix 4.2)
Three RCTs reported symptom reduction after treatment. All studies had very serious limitations and imprecision, e.g. different preconditions in control treatment, unclear randomisation, limitations in blinding, and/or small sample size. Different symptom scales were used to measure PTSD symptoms of which one, used in the study by Kelson (2013), was not validated. Treatment length ranged between 4 weeks and 12 weeks. All studies showed differences in favour of neurofeedback, both regarding the severity of symptoms and the number of patients achieving remission from PTSD (reported in two studies). The intervention groups showed a reduction in PTSD symptoms post-treatment of between 34% and 66%, compared with changes in the control groups ranging from a reduction of 14% to an increase of 13%. Meta-analysis of the pooled data shows a standardised mean difference (SMD) of -2.30 (95% confidence interval -4.37 to -0.24) post-treatment, but with very high heterogeneity (Figure 2).

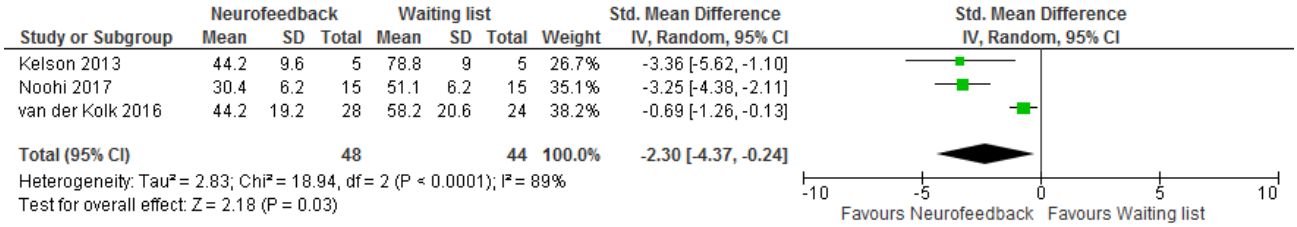

Figure 2. Meta-analysis of self-reported PTSD symptoms after treatment with neurofeedback compared with waiting list.

Follow-up assessment was only done in one of the studies (van der Kolk et al., 2016). At 1 month follow-up, a reduction of PTSD symptoms of 34% on the Davidson Trauma Scale (DTS) was seen after neurofeedback, vs 8% in the control group (p<0.001).

One study (van der Kolk et al., 2016) also measured symptom relief reported on the interview-based Clinician-Administered PTSD Scale (CAPS). Post-treatment, a symptom reduction of 46% was seen in the neurofeedback group versus 13% in the waiting list group (p<0.001). In this study, patients with treatment non-responsive PTSD were included. Both groups continued ongoing treatment during the study period (medication and psychotherapy). At the 1-month follow-up, the symptom reduction from baseline was 51% in the neurofeedback group versus 14% in the waiting list group (p<0.001).

The same study (van der Kolk et al., 2016) also showed that remission one month post-treatment was achieved in 11/19 cases who had received neurofeedback treatment compared with 2/19 in the waiting list group (p=0.002).
Conclusion: It is uncertain whether EEG-based neurofeedback compared with waiting list reduces PTSD symptoms post-treatment in adult patients with PTSD (very low certainty of evidence (GRADE ⊕○○○).

Level of functioning (Appendix 4.3)
One study (Noohi, Miraghaie & Arabi, 2017) measured level of functioning using the Wisconsin Card Sorting Test (WCST), a neuropsychological test of executive functioning, as well as Tower of London (TOL). Both tests assess the ability to plan and adjust actions to stimuli. Measures of both scales favoured neurofeedback compared with the control group ($p<0.001$) (for which no treatment is described in the publication).

Conclusion: It is uncertain whether EEG-based neurofeedback compared with no intervention improves the level of executive cognitive functioning in adult patients with PTSD (very low certainty of evidence, GRADE ⊕○○○).

Health-related quality of life
None of the included studies evaluated health-related quality of life.

Outcomes, important for decision-making

Sick leave/work ability
No study evaluated work ability and one study (van der Kolk et al., 2016) excluded patients with sick leave benefits.

Patients' own experiences of the treatment
None of the included studies examined patients' experiences of the neurofeedback treatment.

Complications
In one study (Kelson, 2013) participants were informed before the neurofeedback treatment about potential complications and continually asked to report any complications or side effects they may experience during or after the neurofeedback treatment, to either the clinician delivering the treatment or to the study coordinator. No participant reported any complications. In the study by van der Kolk et al. (2016), one of 28 patients reported significant side effects after neurofeedback treatment, an increase in flashbacks. In the study by Noohi, Miraghaie and Arabi (2017), patients (number not stated) reported re-experiencing traumatic events and higher-than-normal levels of anxiety and stimulation. Although the risk of complications does not appear to be high, no firm conclusions can be drawn with regard to complications because data on complications were insufficiently collected and/or reported.

9. Ethical aspects

Neurofeedback as treatment for PTSD must be assessed ethically in comparison with other available treatment methods. The question of cost-effectiveness also needs to be addressed. All four included studies showed that neurofeedback seems to reduce symptoms of PTSD, although the certainty of evidence for this finding was assessed to be very low. Notably, all but one of the included studies compared neurofeedback with a control group with no treatment or with patients on a waiting list. The fourth study compared neurofeedback with standard treatment (medication was provided in both treatment groups). So there is only limited information on the comparison with an active control group.

None of the included studies, nor any of the case series that were assessed for inclusion, reported any severe complications. Two of the included studies assessed side effects and reported very few. It is also relevant to note that the treatment protocol in some of the studies included adjustment of the neurofeedback procedure based on patients' self-reported arousal.

However, the cost of the treatment should be considered, as well as what resources are required. The economic analysis shows a slightly increased cost. Patients considered for treatment are often relatively young and therefore may receive rehabilitation to return to work, implying that the potential benefit may outweigh the cost. Another reason to consider this method is that many patients with PTSD do not speak fluent Swedish and may participate more easily in neurofeedback than in EMDR or CBT. An important dilemma might be if neurofeedback would be used instead of more established, guideline-recommended, treatment methods - in absence of established effectiveness (including lack of comparison with sham neurofeedback, to exclude a placebo effect). This could result in patients possibly receiving a treatment with unproven effectiveness at higher cost.

That being said, it is crucial to bear in mind that this is a vulnerable patient group that has experienced difficult events in their lives and is suffering the consequences of these traumas. It is therefore imperative that treatment methods that are effective, accepted and available are assessed in order to provide the best possible care.

In summary, EEG-based neurofeedback is a new technique for treatment of a serious health problem, PTSD, where conventional methods have reached only moderate success. If the results presented in this HTA can be confirmed in a properly designed randomized trial, neurofeedback can be an important alternative for treating these patients.

10. Organisational aspects

Time frame for the putative introduction of the new health technology

Neurofeedback is presently not used in clinical practice at the Sahlgrenska University Hospital in Gothenburg, but necessary preparations have been made so that it can be introduced in the near future. Equipment for EEG neurofeedback has been purchased from research funds, and installed in the facility of an adult psychiatry outpatient clinic. Three healthcare professionals in a trauma team have received training to use the equipment and provide the treatment. The apparatus needs to be tested but is otherwise ready to use. At the Crisis and Trauma Unit, a few patients have been offered the opportunity to try this experimental treatment.

Present use of the technology in other hospitals in Region Västra Götaland

At present there is no routine use of neurofeedback in Region Västra Götaland.

Consequences of the new health technology for personnel

Currently, there are trained personnel available for handling the acquired equipment in a trauma team (one psychologist and two physicians) at a psychiatry outpatient setting, Sahlgrenska University Hospital as well as at the Crisis and Trauma Unit. If neurofeedback should be implemented on a regular and extended basis, additional personnel will be needed. This will require further education and training of personnel.

Consequences for other clinics or supporting functions at the hospital or in the Region Västra Götaland

It is too early to ascertain consequences at this stage. If EEG-based neurofeedback will be shown to be an effective treatment, the number of referrals to clinics where neurofeedback treatment is provided may increase.

11. Economic aspects

Present costs of currently used treatment

Healthcare costs per outpatient visit recorded as PTSD is approximately 3,100 Swedish kronor (SEK). Most patients have a treatment time of between 1-2 years with varying number of sessions, and around 25% of all sessions are "no-shows". Data from the cost per patient database from the Sahlgrenska University Hospital show that the annual outpatient care costs per patient is on average approx. 15,000 SEK, with numbers varying substantially around this average.

Expected costs of the new health technology (see I in PICO)

The expected costs of treatment with EEG neurofeedback is based on a number of resources:

- Investment cost for the computer (110,000 SEK)
- Introductory training fee for personnel (approx. 15,000 SEK per person)
- Displaced care due to absence for introductory training (5 days per person)
- Continued training fee (approx. 10,000 SEK per person)
- Displaced care due to absence for continued training (2 days per person)

The cost per patient of the new health technology also depends on a number of additional parameters: life-length of the equipment, discount rate (used to calculate the total investment costs to annual costs), the degree to which the equipment is used (number of sessions per day and active number of days per year).

Another important factor for the cost regards whether the visits for neurofeedback treatment are add-ons to current treatments, or whether they replace current treatment. If they are add-ons to current treatment, the costs will consist of the technology costs and the costs for the increased number or length of visits. The average cost of a visit is 3,100 SEK, but part of this cost is made up by fixed costs that will not increase if we see a modest increase in the number of visits. We assess that for each additional visit costs increase by at least the labor cost of approx. 650 SEK per hour (physician) or 400 SEK per hour (therapist).

If EEG neurofeedback treatment replaces current treatments, the costs will consist of the technology costs alone. We calculated the annual healthcare costs for the EEG neurofeedback technology (per each computer) for two alternative ways of implementing the technology: that it is used as an add-on to current treatment methods and that it completely replaces current treatments. For both alternatives, we calculated a low- and a high-cost scenario (Table 1); the true estimate will most likely be somewhere between these bounds based on how clinical practice changes.

Table 1. Estimated costs for the EEG neurofeedback technology if replacing or adding to current treatment options.

	If 100% add-on to current treatment		**If 100% replacing current treatment**	
	Low-cost scenario	*High-cost scenario*	*Low-cost scenario*	*High-cost scenario*
Life-length computer	7	5	7	5
Discount rate	3%	4%	3%	4%
Investment cost (computer)	110,000 SEK	110,000 SEK	110,000 SEK	110,000 SEK
Training costs	25,000 SEK (1 person)	50,000 SEK (2 persons)	25,000 SEK (1 person)	50,000 SEK (2 persons)
Value of displaced care	19,000 SEK (1 person)	38,000 SEK (2 persons)	19,000 SEK (1 person)	38,000 SEK (2 persons)
Sessions per day	3	2	3	2
Active days per year	200	175	200	175
Labor costs (per visit)	400 SEK	650 SEK	-	-
Added cost per each session/visit	**453 SEK**	**731 SEK**	**53 SEK**	**81 SEK**

The added cost for each session/visit is approximately 453 to 731 SEK if EEG neurofeedback treatment is added to current treatment, and 53 to 81 SEK if it replaces current treatment.

Total change in costs

The total increase in annual healthcare costs depends on the size of the investment (in terms of number of computers) and if treatments with the EEG neurofeedback technology replaces current treatments or offered as add-on to current treatments.

Assuming each of the four units in which patients with PTSD are treated in VGR invests in one computer each, the increase in total costs from the investment will be in the range of 85,000 to 171,000 SEK per year. Additionally, health care costs will increase substantially more if EEG neurofeedback treatments are used as add-on to current treatments. The total change in costs will depend on the number of patients treated and number of additional visits, both of which are unknown parameters at this time.

There is a potential cost-saving aspect of the EEG neurofeedback technology as well; if the neurofeedback treatment is more effective compared with current treatments, this may reduce treatment times and thus reduce total costs, although we have no data at this point to assess such potential effects quantitatively.

Possibility to adopt and use the new technology within the present budget

The new technology will, presuming no change in the number or length of visits, result in increased healthcare costs as outlined above, and there is no possibility to adopt and use the new technology within the present budget. The present budget will have to be increased or the new technology will lead to displacement of some other care.

Available economic evaluations or cost advantages/disadvantages

No economic evaluations or cost-consequence or budget-impact analysis studies of the new technology were identified in the published literature.

12. Discussion

Summary of main results

The findings of the four, small, studies included in this HTA report, suggest that treatment with EEG-based neurofeedback seem to improve PTSD symptoms in adult patients with PTSD. When data from the individual studies were pooled in meta-analysis, the effect size shown was very large, SMD 2.3. Normally an SMD above 0.8 is considered a large effect size (Cohen, 1988). However, due to study limitations, some indirectness and imprecision, our confidence in this finding is very low (GRADE ⊕◯◯◯). In addition, no sham-controlled study was identified, which implies that a placebo effect cannot be excluded. This means that we cannot draw any firm conclusions about the effects of the neurofeedback interventions. As to the other outcomes evaluated in the included studies, it is uncertain whether suicidal thoughts, executive functioning or medication use are affected, with certainty of evidence for these findings being very low (GRADE ⊕◯◯◯).

Overall completeness and applicability of evidence

All included studies show results in favour of EEG neurofeedback. However, the findings are based on few and small studies with several study limitations, and there is also uncertainty with regard to directness. Three of the four studies involved only men, while in the fourth, the majority were women. In two studies, the participants were war veterans; in one of them they were homeless war veterans in the United States.

These settings and populations limit the applicability of the evidence to the Swedish healthcare setting. Although complications were not systematically addressed in the included studies, this HTA report did not find any indication of serious complications of the treatment.

Study limitations

A major problem with the underlying studies is that none of the studies compared neurofeedback to sham neurofeedback. Since no sham-controlled study was identified, the effect could be entirely attributable to a placebo effect. Three of the studies compared EMG neurofeedback with a non-active waiting list and only one study compared with standard treatment (note –medication was provided in both treatment groups). There also is concern that the drop-out rate in some of the studies might influence the results; however, it should be noted that this is a vulnerable patient group that may be predisposed to other factors interfering with possibilities of completing treatment. Another problem is that the intervention often consists of EEG neurofeedback in combination with mindfulness-/meditation-related exercises. Furthermore, there is a variability in the intensity and dose of neurofeedback treatment and protocols in the different studies, with some delivering daily treatment and others less frequent sessions, the duration of treatment varies, and the number of sessions differed between studies. All included studies were small and had problems with internal validity as well as precision, limiting our confidence in the effect estimates.

Agreements and disagreements with other studies and reviews

The findings of this HTA report are in agreement with three systematic reviews, which all interpret the evidence as limited but indicate positive effects of neurofeedback in patients with PTSD (Banerjee & Argaez, 2017, Reiter et al., 2016, Panish & Hai, 2018). The three reviews did not, however, include all four RCTs that were analysed in this report. The review by Banerjee & Argaez (2017) (a Canadian HTA) is based on van der Kolk et al. (2016), the review by Reiter et al. (2016) used data from the RCT by Peniston & Kulkolsky (1991), and the newest review by Panisch & Hai (2018) included three of the four RCTs included in this HTA report.

The effect size of the symptom reduction that was shown in the meta-analysis can be compared with two recent Cochrane reviews of other interventions for patients with PTSD (Lewis et al., 2018, Cramer et al., 2018).
One showed an effect size for internet-based cognitive therapy compared with waiting list of SMD -0.60 (95% CI -0.97 to -0.24) (Lewis et al 2018), while the other showed an effect size for yoga, a method that often incorporates meditation-related exercises, compared with waiting list of SMD -1.10 (95% CI -1.72 to - 0.47). In comparison with these reviews, the effect size for neurofeedback compares favourably. Our findings are also in line with the recently published NICE guideline on non-pharmacological interventions for adult patients with PTSD (National Institute for Health and Care Excellence, 2018). The guideline authors also conclude that there is low to very low evidence that neurofeedback results in large and statistically significant benefits in patients with PTSD on improving PTSD symptoms.

Implications for research

The findings of this report suggest a need for further intervention studies of EEG-based neurofeedback for patients with PTSD, especially in light of recent migration patterns of people who have been exposed to war trauma. Future studies should be rigorously designed and ideally compare neurofeedback with sham neurofeedback. A comparison of the number of sessions to symptom reduction for a stepwise analysis might give further indications of whether the reported effects can be attributed to the neurofeedback treatment. Moreover, to achieve detailed knowledge that can assist professionals' decision making in individual PTSD treatments, studies on *when* (e.g. timing in relation to key life factors) and for *whom* (e.g. gender, age, stress levels) the treatment would be beneficial, as well as studies that evaluate important outcomes such as suicidality, health-related quality of life and complications. Furthermore, information on long-term effects of neurofeedback treatment for patients with PTSD is lacking and would be relevant to study.

13. Future perspectives

Scientific knowledge gaps

A number of issues need to be addressed in future studies:

- Is the observed effect due to neurofeedback or to a placebo effect (extra effort and attention involved, i.e. the extra number of sessions with a healthcare provider)?
- Is the effect of neurofeedback specific to the EEG feedback and not to mindfulness exercises?
- Are there less costly ways to perform neurofeedback (fewer sessions, at home etc.)?

EEG-based neurofeedback thus needs to be tested in well-designed studies before being considered for treating patients in routine care. Most importantly, an RCT in which EEG-based neurofeedback is compared with sham neurofeedback or active treatment should be designed, and is currently under planning.

Ongoing research

In our search for ongoing trials, we identified one relevant study. This study, designed to compare neurofeedback with sham-neurofeedback, was completed in 2016. However, no publication of the study could be found.

14. Participants in the project

The question was nominated by
Britt Tallhage, manager Crisis and Trauma Unit, Region Västra Götaland, Gothenburg, Sweden

Participating healthcare professionals
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Administrative support
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Declaration of interests
The authors declare no conflicts of interest.

Project time
The HTA was accomplished during the period of 6 November 2018 – 15 April 2019.
Literature searches were made on 16 November 2018.

Appendix 1: PICO, study selection, search strategies, and references

Question(s) at issue:
Is EEG-based neurofeedback as treatment for patients with post-traumatic stress disorder effective on self harm, PTSD symptoms, level of functioning and health-related quality of life compared with sham neurofeedback, other treatment, or no treatment?

PICO: (*P=Patient I=Intervention C=Comparison O=Outcome*)

P: Adult (≥18 years) patients diagnosed with PTSD

I: EEG biofeedback/neurofeedback (alone or in combination with other treatment)

C1: Sham neurofeedback
C2: Other treatment (e.g. psychotherapy, medication, physiotherapy, eye movement desensitisation and reprocessing (EMDR))
C3: No treatment

O:

Critical for decision making

- Self harm, including suicidality (both self-reported and observed behaviour, e.g. hospital visits) and suicidal thoughts
- PTSD symptoms measured with validated instruments
- Level of functioning measured with validated instruments
- Health-related quality of life measured with validated instruments

Important for decision making

- Sick leave/work ability
- Medication use
- Patients' experiences of the treatment
- Complications

Eligibility criteria

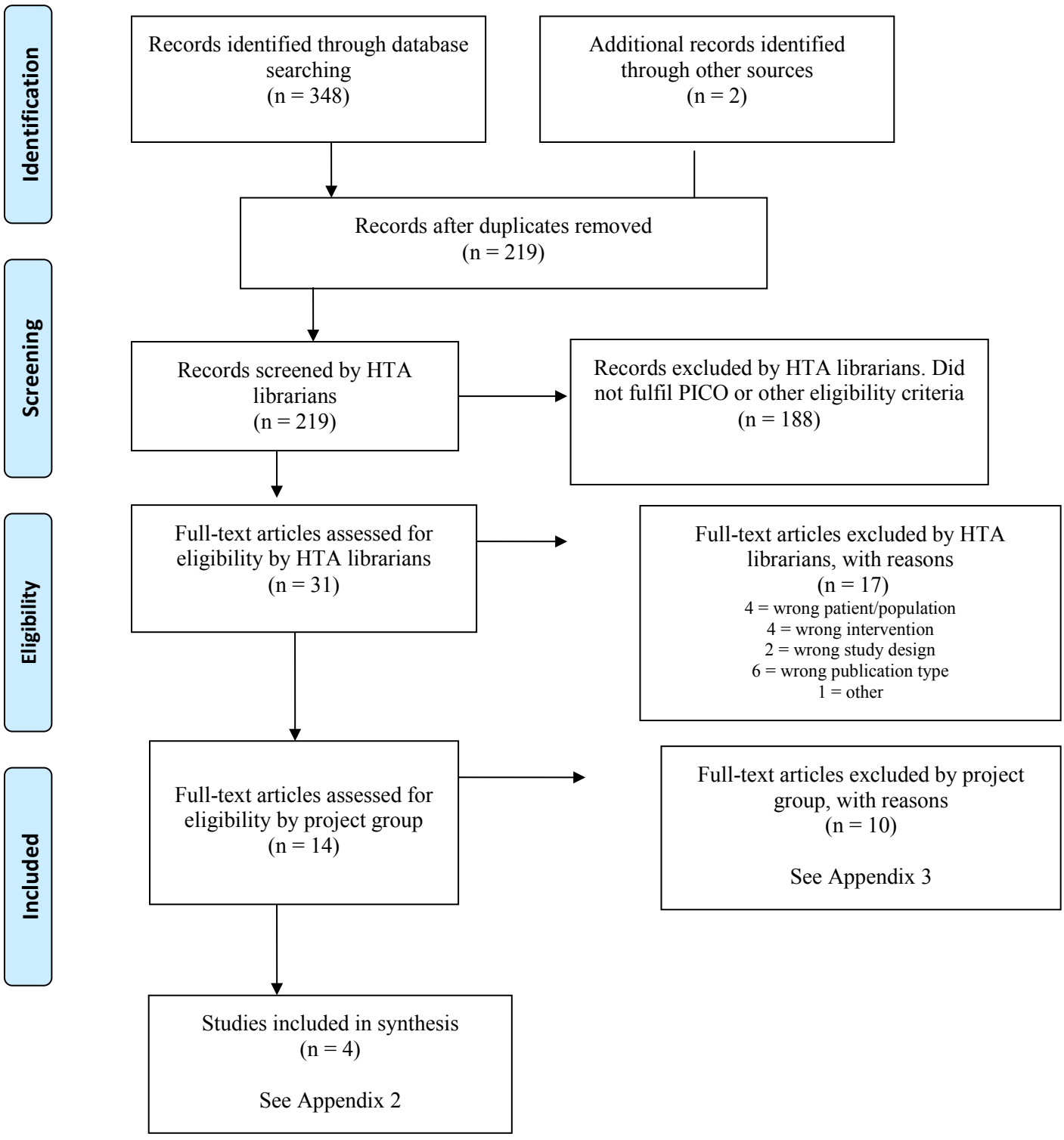
Study design:
RCT, cohort studies, case series with ≥ 10 pat (for analysis of complications), qualitative studies, cost/economic studies.

Systematic reviews published from 2016 were included in search for purposes of scrutinising reference lists, but not included in analysis.

Language:
English, Swedish, Norwegian, Danish

Publication date: -

Selection process – flow diagram



Modified from Moher et al., 2009

Search strategies

Database: PubMed
Date: 16 Nov 2018
No. of results: 45

Search	Query	Items found
#9	**Search #4 AND #7 Filters: Danish; English; Norwegian; Swedish**	**45**
#8	Search #4 AND #7	47
#7	Search #5 OR #6	42687
#6	Search (PTSD[tiab] OR ((post-traumatic[tiab] OR posttraumatic[tiab]) AND (stress[tiab] OR neuroses[tiab] OR neurosis[tiab] OR disorder*[tiab])))	34464
#5	Search Stress Disorders, Post-Traumatic[mh]	28933
#4	Search #1 OR #2 OR #3	8910
#3	Search ((brainwave[tiab] OR alpha[tiab] OR electromyography[tiab] OR electromyographic[tiab] OR EEG[tiab] OR electroencephalography[tiab] OR electroencephalographic[tiab]) AND (biofeedback*[tiab] OR feedback*[tiab] OR bio-feedback*[tiab]))	7766
#2	Search (neurofeedback[tiab] OR neuro-feedback[tiab])	1215
#1	Search Neurofeedback[mh]	666

Database: Embase 1974 to 2018 November 15 (OvidSP)
Date: 16 Nov 2018
No. of results: 117

#	Searches	Results
1	exp neurofeedback/	2327
2	(neurofeedback or neuro-feedback).ab,ti.	1883
3	(brainwave or alpha or electromyography or electromyographic or EEG or electroencephalography or electroencephalographic).ab,ti.	1085536
4	(biofeedback* or feedback* or bio-feedback*).ab,ti.	160095
5	3 and 4	8938
6	1 or 2 or 5	11253
7	exp posttraumatic stress disorder/	51823
8	(PTSD or ((post-traumatic or posttraumatic) and (stress or neuroses or neurosis or disorder*))).ab,ti.	42969
9	7 or 8	59830
10	6 and 9	121
12	**limit 10 to (danish or english or norwegian or swedish)**	**117**

Database: CINAHL (EBSCOhost)
Date: 16 Nov 2018
No. of results: 19

#	Undran	Resultat
S7	**S3 AND S6** **Limit, Language: english**	**19**
S6	S4 OR S5	22,459
S5	TI (PTSD OR ((post-traumatic OR posttraumatic) AND (stress OR neuroses OR neurosis OR disorder*))) OR AB (PTSD OR ((post-traumatic OR posttraumatic) AND (stress OR neuroses OR neurosis OR disorder*)))	14,831
S4	(MH "Stress Disorders, Post-Traumatic+")	18,601
S3	S1 OR S2	1,225
S2	TI ((brainwave OR alpha OR electromyography OR electromyographic OR EEG OR electroencephalography OR electroencephalographic) AND (biofeedback* OR feedback* OR bio-feedback*)) OR AB ((brainwave OR alpha OR electromyography OR electromyographic OR EEG OR electroencephalography OR electroencephalographic) AND (biofeedback* OR feedback* OR bio-feedback*))	835
S1	TI (neurofeedback OR neuro-feedback) OR AB (neurofeedback OR neuro-feedback)	449

Database: PsycINFO (EBSCOhost)
Date: 16 Nov 2018
No. of results: 51

#	Undran	Resultat
S8	**S4 AND S7** **Limit, language: Danish, English, Norwegian, Swedish** **Exclude, Publication Type: Doctoral Dissertation**	**51**
S7	S5 OR S6	42,734
S6	TI (PTSD OR ((post-traumatic OR posttraumatic) AND (stress OR neuroses OR neurosis OR disorder*))) OR AB (PTSD OR ((post-traumatic OR posttraumatic) AND (stress OR neuroses OR neurosis OR disorder*)))	40,447
S5	(DE "Posttraumatic Stress Disorder" OR DE "Complex PTSD" OR DE "DESNOS")	29,970
S4	S1 OR S2 OR S3	3,745
S3	TI ((brainwave OR alpha OR electromyography OR electromyographic OR EEG OR electroencephalography OR electroencephalographic) AND (biofeedback* OR feedback* OR bio-feedback*)) OR AB ((brainwave OR alpha OR electromyography OR electromyographic OR EEG OR electroencephalography OR electroencephalographic) AND (biofeedback* OR feedback* OR bio-feedback*))	2,332
S2	TI (neurofeedback OR neuro-feedback) OR AB (neurofeedback OR neuro-feedback)	1,296
S1	DE "Neurotherapy"	1,359

Database: Web of Science
Date: 16 Nov 2018
No. of results: 91

Set	Results	
# 6	**91**	**#4 AND #3** **Refined by: LANGUAGES: (ENGLISH)** **Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI** **Timespan=All years**
# 5	96	#4 AND #3 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI Timespan=All years
# 4	59,171	TOPIC: (PTSD OR ((post-traumatic OR posttraumatic) AND (stress OR neuroses OR neurosis OR disorder*))) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI Timespan=All years
# 3	16,259	#2 OR #1 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI Timespan=All years
# 2	14,738	TOPIC: ((brainwave OR alpha OR electromyography OR electromyographic OR EEG OR electroencephalography OR electroencephalographic) AND (biofeedback* OR feedback* OR bio-feedback*)) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI Timespan=All years
# 1	2,078	TOPIC: (neurofeedback OR neuro-feedback) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI Timespan=All years

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Database: The Cochrane Library
Date: 16 Nov 2018
No. of results: 25
Cochrane Reviews (0)
Cochrane Protocols (0)
Trials (25)
Editorials (0)
Special Collections (0)
Clinical Answers (0)
Other Reviews (0)

ID	Search	Hits
#1	MeSH descriptor: [Neurofeedback] explode all trees	123
#2	(neurofeedback OR neuro-feedback):ti,ab,kw (Word variations have been searched)	470
#3	((brainwave OR alpha OR electromyography OR electromyographic OR EEG OR electroencephalography OR electroencephalographic) AND (biofeedback* OR feedback* OR bio-feedback*)):ti,ab,kw (Word variations have been searched)	1097
#4	#1 OR #2 OR #3	1449
#5	MeSH descriptor: [Stress Disorders, Post-Traumatic] explode all trees	2038
#6	(PTSD OR ((post-traumatic OR posttraumatic) AND (stress OR neuroses OR neurosis OR disorder*))):ti,ab,kw (Word variations have been searched)	4492
#7	#5 OR #6	4492
#8	**#4 AND #7**	**25**

The web-sites of **SBU** and **Folkehelseinstituttet** were visited 16 Nov 2018.
Nothing relevant to the question at issue was found

Reference lists
A comprehensive review of reference lists brought **2** new records.

Reference lists

Included studies:

Kelson CY. The Impact of EEG Biofeedback on Veterans' Symptoms of Posttraumatic Stress Disorder (PTSD): The Chicago School of Professional Psychology; 2013.

Noohi S, Miraghaie AM, Arabi A. Effectiveness of neuro-feedback treatment with alpha/theta method on PTSD symptoms and their executing function. Biomed Res (Aligarh). 2017;28(5):2019-27.

Peniston EG, Kulkosky PJ. Alpha-theta brainwave neuro-feedback therapy for Vietnam veterans with combat-related post-traumatic stress disorder. Medical psychotherapy. 1991;4:47-60.

van der Kolk BA, Hodgdon H, Gapen M, Musicaro R, Suvak MK, Hamlin E, et al. A Randomized Controlled Study of Neurofeedback for Chronic PTSD. PLoS One. 2016;11(12):e0166752.

Excluded studies:

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Project: EEG-based neurofeedback for patients with post-traumatic stress disorder

Appendix 2 – Characteristics of included studies

Author Year Country	Study design	Length of follow-up	Study groups; Intervention vs control	Patients (n)	Mean age (years)	Men (%)	Outcome variables
Kelson 2013 USA	RCT	Final assessment at end of 4 week treatment	I: EEG-based neurofeedback: 20 sessions, 5 times/week during 4 weeks C: waiting list (offered EEG-based neurofeedback at end of study)	Veterans with PTSD diagnosis I: 7 C: 5	I: 53.8 C: 49.8	100%	- PTSD symptoms, measured with self-constructed scale based on symptoms included in diagnostic criteria - Suicidal thoughts, measured in one item in PTSD symptom scale
Noohi 2017 Iran	RCT	Final assessment at end of 45 day treatment	I: EEG-based neurofeedback: 25 sessions, 4 times/week during 45 days C: no intervention (?)	Patients with PTSD I: 15 C: 15	25-60 (mean not reported)	100%	- PTSD symptoms, measured with the Impact of event scale-revised (IES-R) - Level of functioning, measured with cognitive performance tests
Peniston 1991 USA	RCT	30 months after treatment	I: EEG-based neurofeedback: 30 sessions, 5 times/week C: standard treatment (traditional medical control, i.e. psychotropic medication and individual and group therapy) In both groups a reduction of the initial psychotropic medication dosage was attempted	Veterans with chronic PTSD I: 15 C: 14	I: 36.1 (SD 2.6) C: 37.2 (SD 2.8)	100%	- PTSD symptoms, measured with the Minnesota Multiphasic Personality Inventory (MMPI) PTSD scale - Psychotropic medication dosage
van der Kolk 2016 USA	RCT	4 weeks after end of 12 week treatment	I: Initial pre-training in temperature biofeedback followed by EEG-based neurofeedback: 24 sessions 2 times/week for 12 weeks C: waiting list Both groups continued ongoing treatment (medication and psychotherapy)	Adults with treatment nonresponsive PTSD I: 28 C: 24	I: 46.0 (SD: 12.9) C: 42.4 (SD: 13.5)	24%	- PTSD symptoms, measured with the Clinician administered PTSD scale (CAPS) and the Davidson Trauma Scale (DTS)

Project: EEG-based neurofeedback treatment of patients with post-traumatic stress disorder
Appendix 3.
Excluded studies

Author, year	Reason for exclusion
Banerjee, 2017	Wrong publication type
Gapen, 2016	Case series not reporting complications
Johnson, 2013	Wrong population, not possible to separate PTSD
Kluetsch, 2014	Wrong outcome
McReynolds, 2017	Case series not reporting complications
Nicholson, 2016	Case series not reporting complications
Panisch, 2018	Wrong publication type
Peniston, 1993	Case series not reporting complications
Reiter, 2016	Wrong publication type
Ros, 2017	Wrong population, healthy adults

Project: EEG-based neurofeedback for patients with post-traumatic stress disorder

*	+ No or minor problems
	? Some problems
	- Major problems

Appendix 4.1

Outcome variable: Self harm, including suicidality (both self-reported and observed behaviour, e.g. hospital visits) and suicidal thoughts

Author year country	Study design	Number of patients n=	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention Neurofeedback	Control Waiting list				
Kelson 2013	Randomised controlled trial	I: 7 C: 5	2 in the intervention group	<u>Suicidal thoughts</u> Pre: 2.2 (SD 0.8) Post (week 4): 1.0 (SD 0.0) Δ -1.2	<u>Suicidal thoughts</u> Pre: 1.0 (SD 0.0) Post (week 4): 1.2 (SD 0.45) Δ 0.2 *Between-group difference in pre-to-post change:* *Δ: -1.4* *p=0.002*	Difference was due to 3 patients out of 10. NB: the question is rated 1-5, 1 being the lowest possible answer (no suicidal thoughts).	-	?	-

Project: EEG-based neurofeedback for patients with post-traumatic stress disorder

* + No or minor problems
? Some problems
- Major problems

Appendix 4.2
Outcome variable: PTSD symptoms, measured with validated instruments

Author Year Country	Study design	Number of patients n=	Withdrawals - dropouts	Results		Comments	Directness*	Study limitations*	Precision*
				Intervention EEG neurofeedback	Control Waiting list or standard treatment				
Kelson 2013 USA	Randomised controlled trial	I: 7 C: 5	I: 2	PTSD symptoms questionnaire Pre: 72.8 (SD 12.6) Post (week 4): 44.2 (SD 9.6) Δ -28.6	PTSD symptoms questionnaire Pre: 69.4 (SD 10.0) Post (week 4): 78.8 (SD 9.0) Δ +9.4 *Between-group difference in pre-to-post change:* *Δ -38.0, p<0.01*	23-item instrument ranging from 23 to 115, lower values indicate fewer symptoms. NB: The PTSD symptoms questionnaire is not a validated instrument.	-	?	-
Noohi 2017 Iran	Randomised controlled trial	I: 15 C: 15	0?	IES-R Pre: 47.2 (SD 7.6) Post (45 days): 30.4 (SD 6.2) Δ -16.8	IES-R Pre: 51.1 (SD 5.4) Post (45 days): 51.1 (SD 6.2) Δ 0.0 *Between-group difference in pre-to-post change:* *Δ -16.8, p<0.001*	Number of withdrawals unclear. 22-item instrument, ranging from 0 to 88, lower values indicate fewer symptoms.	+	-	?
Peniston 1991 USA	Randomised controlled trial	I: 15 C: 14	0	MMPI PTSD Pre: 30.6 (SD 9.1) Post (28 days):10.5 (SD 6.2) Δ -20.1 PTSD relapse after 30 months Relapse: 3/15 (20%)	MMPI PTSD Pre: 35.9 (SD 7.2) Post (28 days): 36.2 (SD 5.3) Δ +0.3 *Between-group difference in pre-to-post change:* *Δ -20.4, p<0.05* PTSD relapse after 30 months Relapse: 14/14 (100%) *Between-group difference in pre-to-post change:* *-80%, p<0.05*	MMPI PTSD is a scale based on 49 items related to PTSD that are part of a larger number of personality measures. The range of the scale is 0-49, lower values indicate fewer symptoms. NB: Numbers for MMPI PTSD measured on a graph (not reported in article)	?	?	?

Project: EEG-based neurofeedback for patients with post-traumatic stress disorder

* + No or minor problems
? Some problems
- Major problems

Appendix 4.2
Outcome variable: PTSD symptoms, measured with validated instruments

Author Year Country	Study design	Number of patients n=	Withdrawals - dropouts	Results		Comments	Directness*	Study limitations*	Precision*
				Intervention EEG neurofeedback	Control Waiting list or standard treatment				
van der Kolk 2016 USA	Randomised controlled trial	I: 28 C: 24	I: 6 C: 2	<u>DTS</u> Pre: 67.3 (SD 25.0) Post: 44.2 (SD 19.2) Δ -23.1 (-34.3%) 1 month follow-up: 36.5 (SD 19.3) Δ -30.8 <u>CAPS</u> Pre: 79.5 (SD 16.9) Post: 43.0 (SD 20.2) Δ -36.5 (-45.9%) 1 month follow-up: 39.1 (SD 20.0) Δ -40.4 (-50.8%)	<u>DTS</u> Pre: 63.0 (SD 18.2) Post: 58.2 (SD 20.6) Δ -4.8 (-7.6%) *Between-group difference in pre-to-post change:* *Δ -13.4, p<0.001* 1 month follow-up: 65.5 (SD 20.3) Δ +2.5 *Between-group difference in pre-to-1 month post change:* *Δ -33.3, p<0.001* <u>CAPS</u> Pre: 76.2 (SD 16.9) Post: 66.5 (SD 20.6) Δ -9.7 (-12.7%) *Between-group difference in pre-to-post change:* *Δ -26.8, p<0.001* 1 month follow-up: 65.5 (SD 20.3) Δ -10.8 (-14.2%) *Between-group difference in pre-to-1 month post change:* *Δ -29.6, p<0.001*	DTS ranges from 0 to 136, lower values indicate fewer symptoms. 95% CIs reported in the paper converted to SD. CAPS ranges from 0 to 136, lower values indicate fewer symptoms. A score under 45 is considered as not meeting criteria for PTSD. A 20-point change in CAPS criteria indicates a clinically significant change. 95% CIs reported in the paper converted to SD.	+	+	+

Project: EEG-based neurofeedback for patients with post-traumatic stress disorder

* + No or minor problems
? Some problems
- Major problems

Appendix 4.2
Outcome variable: PTSD symptoms, measured with validated instruments

Author Year Country	Study design	Number of patients n=	Withdrawals - dropouts	Results		Comments	Directness*	Study limitations*	Precision*
				Intervention EEG neurofeedback	Control Waiting list or standard treatment				
				<u>Remission</u> Remission at week 12 (post-treatment): 16/22 (73%) Remission at week 16: 11/19 (58%)	<u>Remission</u> Remission at week 12 (post-treatment): 7/22 (32%) *Between-group difference: 41%, p=0.007* Remission at week 16: 2/19 (10%) *Between-group difference: 48%, p=0.002*				

PTSD: Post-traumatic stress disorder; IES-R: Impact of event scale-revised; MMPI: Minnesota Multiphasic Personality Inventory; CAPS: Clinician administered PTSD scale; DTS: Davidson Trauma Scale
Note: A negative between-group difference in change indicates a difference in favour of neurofeedback

Project: EEG-based neurofeedback for patients with post-traumatic stress disorder

* + No or minor problems
? Some problems
- Major problems

Appendix 4.3
Outcome variable: Level of functioning measured with validated instruments

Author year country	Study design	Number of patients n=	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention EEG-based neurofeedback	Control No intervention				
Noohi 2017 Iran	Randomised controlled trial	30	0	<u>Wisconsin Card Sorting Test</u> Number of errors: Baseline: 75.7 (SD 22.7) After 45 days: 19.2 (SD 15.3) Δ -56.5 Perseveration response: Baseline: 49.8 (SD 18.0) After 45 days: 9.7 (SD 9.0) Δ -40.1 Numbers of categories: Baseline: 2.5 (SD 1.8) After 45 days: 5.6 (SD 0.7) Δ +3.1 <u>Tower of London</u> Score: Baseline: 22.0 (SD 5.0) After 45 days: 28.1 (SD 3.2) Δ +6.1	<u>Wisconsin Card Sorting Test</u> Number of errors: Baseline: 73.7 (SD 21.4) After 45 days: 46.6 (SD 25.0) Δ -27.1 *Between-group difference in pre-to-post change:* *Δ -29.4, p<0.001* Perseveration response: Baseline: 50.4 (SD 17.9) After 45 days: 26.5 (SD 18.5) Δ -23.9 *Between-group difference in pre-to-post change:* *Δ -16.2, p<0.001* Numbers of categories: Baseline: 3.2 (SD 1.7) After 45 days: 4.2 (SD 1.7) Δ +1.0 *Between-group difference in pre-to-post change:* *Δ +2.1, p<0.001* <u>Tower of London</u> Score: Baseline: 23.3 (SD 5.1) After 45 days: 23.3 (SD 3.1) Δ 0 *Between-group difference in pre-to-post change:* *Δ +6.1, p<0.001*	Both measures are well established cognitive performance tests that assess executive functioning. - Number of errors in WCST indicates rate of success in identifying a pattern. A lower score indicates a better result. - Perseveration response indicates how well an individual adjusts to a changed situation. A lower score indicates a better result. - Number of categories is a measure of how many tests an individual makes in the given time frame. In TOL a higher score indicates a better result. Both tests measure the actual number, which theoretically can be between 0 and infinity.	+	-	?

WCST, Wisconsin Card Sorting Test; TOL, Tower of London.

Project: EEG-based neurofeedback for patients with post-traumatic stress disorder

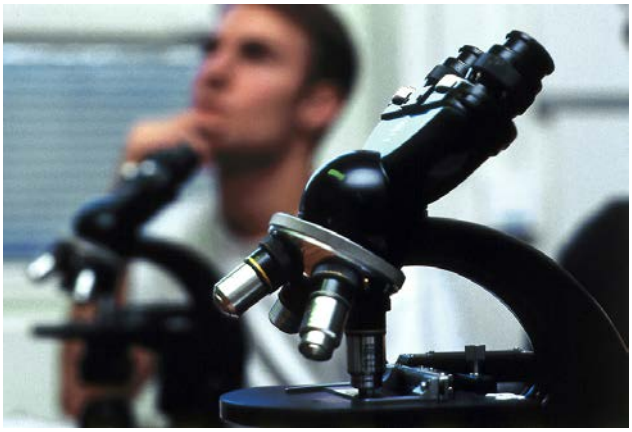
* + No or minor problems
? Some problems
- Major problems

Appendix 4.4
Outcome variable: Medication use

Author year country	Study design	Number of patients n=	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention EEG neurofeedback	Control Standard treatment				
Peniston 1991 USA	Randomised controlled trial	I: 15 C: 14	I: 1* C:1*	Number of patients with decrease in medication use Decrease: 14/14	Number of patients with decrease in medication use Decrease: 1/13 *Between group difference:* $\chi^2 = 23.26$ $p<0.05$	*Evaluation not applicable for 2 patients who did not receive medication from start. All patients in both groups tried tapering off medication at start of trial.	?	?	?

Region Västra Götaland, HTA-centrum

Health Technology Assessment
Regional activity-based HTA



HTA

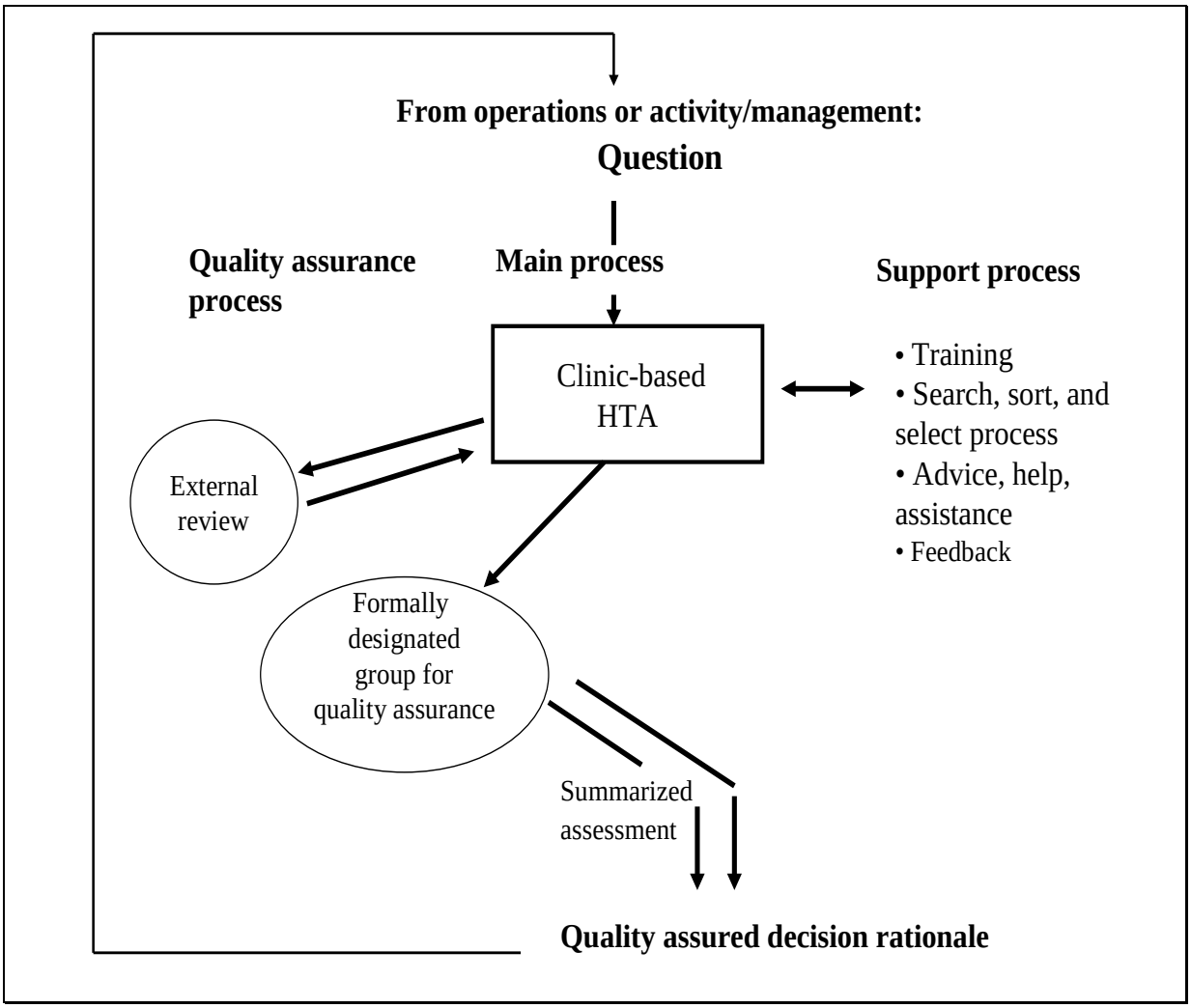
Health technology assessment (HTA) is the systematic evaluation of properties, effects, and/or impacts of health care technologies, i.e. interventions that may be used to promote health, to prevent, diagnose or treat disease or for rehabilitation or long-term care. It may address the direct, intended consequences of technologies as well as their indirect, unintended consequences. Its main purpose is to inform technology-related policymaking in health care.

To evaluate the quality of evidence the Centre of Health Technology Assessment in Region Västra Götaland is currently using the GRADE system, which has been developed by a widely representative group of international guideline developers. According to GRADE the level of evidence is graded in four categories:

High quality of evidence	= (GRADE⊕⊕⊕⊕)
Moderate quality of evidence	= (GRADE ⊕⊕⊕O)
Low quality of evidence	= (GRADE ⊕⊕OO)
Very low quality of evidence	= (GRADE ⊕OOO)

In GRADE there is also a system to rate the strength of recommendation of a technology as either “strong” or “weak”. This is presently not used by the Centre of Health Technology Assessment in Region Västra Götaland. However, the assessments still offer some guidance to decision makers in the health care system. If the level of evidence of a positive effect of a technology is of high or moderate quality it most probably qualifies to be used in routine medical care. If the level of evidence is of low quality the use of the technology may be motivated provided there is an acceptable balance between benefits and risks, cost-effectiveness and ethical considerations. Promising technologies, but a very low quality of evidence, motivate further research but should not be used in everyday routine clinical work.

Christina Bergh, Professor, MD.
Head of HTA-centrum


From operations or activity/management:
Question
Quality assurance process
Main process
Support process
Clinic-based HTA
• Training
• Search, sort, and select process
• Advice, help, assistance
• Feedback
External review
Formally designated group for quality assurance
Summarized assessment
Quality assured decision rationale

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