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SYSTEMATIC REVIEW

QUANTITATIVE EEG AS OUTCOME MEASURE OF THE THERAPEUTIC EFFECTS OF TRANSCRANIAL PHOTOBIOMODULATION: A SYSTEMATIC REVIEW

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Abstract

Background: Transcranial Photobiomodulation (t-PBM) is a current, innovative method that is used in the therapy of many neurological and psychological diseases. Its mechanisms of action have been investigated and the most well described ways of action are its effects on mitochondrial function and on heat/light-activated ion channels on neurons membrane. It has been suggested that the increase in cerebral blood flow and the alterations of membrane ion channels are the most dominant potential mechanisms that cause the effects of PBM on quantitative electroencephalography (qEEG), that some recent studies have reported.

Aim: The aim of this review is to describe the effects that t-PBM has on brain oscillations, as these are measured by qEEG.

Methods: The research was carried out in the Pubmed database and it included all studies that had been published until February 2022.

Results: Overall, sixty-eight studies were located and considered, searching with the terms *Photobiomodulation* or *Light Therapy* or *Near Infrared Light* and *EEG*. Only eleven of them used Photobiomodulation in order to observe the effect it can have on human brain oscillations, measured by qEEG. Two studies reported the EEG alterations after t-PBM application on the hand instead of the head. Thus, nine studies were included in the review, which applied t-PBM and observed the alterations that it brought upon qEEG of healthy adults or patients with memory problems.

Conclusion: The studies showed that t-PBM increases high frequency neural activity and inhibits low frequency oscillations. The studies varied a lot in the ways of light application and the parameters of the light itself, as well as on their study population.

Keywords: Photobiomodulation therapy, low-level light therapy, electroencephalogram, brain oscillations, cognitive impairment, brain function.

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INTRODUCTION

Transcranial Photobiomodulation (t-PBM) refers to the absorption of photons by the cerebral cortex, using near-infrared (NIR) laser or light- emitting diodes (LEDs). The impact of light therapy on the neurons is associated with the upregulation of mitochondrial function,[1] through the increased activity of complexes in the respiratory chain. The absorption of radiation by chromophores, which are photoacceptor molecules that absorb photons, leads to photochemical reactions. Cytochrome c oxidase (CCO) is the terminal enzyme of the mitochondrial respiratory chain and serves as photoacceptor molecule. Its activation increases mitochondrial membrane potential, leading to acceleration of electron transport and an increase of ATP synthesis and oxygen consumption.[1-3]

Also, the activation of light-activated ion channels in the brain cellular membrane[2] leads to the enhancement of the metabolic energy of neurons,[3-4] the increase of intracellular [Ca+],[5] the increase of the cerebral blood flow,[6-7]the activation of signaling pathways and the increased genes expression and cell migration[8]. Furthermore, recent publications showed that t-PBM has anti-inflammatory, anti-apoptotic and antioxidant impact on the human cells.[9-10] It is reported that light can enhance antioxidant defense system, increasing antioxidants production, such as glutathione, superoxide dismutase and catalase.[11]

There has been some research on the impact Photobiomodulation can have on human brain oscillations, observing the changes on the EEG after a t-PBM session. As an attempt to understand and explain the positive effect of t-PBM on human cognition, scientists have used EEG and recorded the alterations of the brain waves, using various ways of delivering light to the brain cortex.

MATERIALS AND METHODS

Research Strategy

The primary search was conducted until the end of February 2022. The database of PubMED was searched for studies on the impact of Photobiomodulation on the human brain oscillations, using the keywords "Photobiomodulation", "Laser light therapy", "Near Infrared light" "Electroencephalography" and "Electroencephalogram". The articles' titles, abstracts and full-texts were screened and assessed against the inclusion and exclusion criteria. The search was limited to original clinical studies either on healthy adults or on patients with self-reported memory complaints or on adults with dementia/ cognitive decline diagnosis. Also, only publications in English were searched.

Inclusion/exclusion Criteria

We included all clinical studies reporting the effects of the laser light or photobiomodulation on the EEG, excluding the articles where the application of laser light or LED was not on the human brain, (either transcranial or intranasal). We recorded the light source, irradiance time, EEG recording time before, after, or even during the irradiation, the wavelength(s), the operation mode (continuous or pulsed), the number of treatment sessions and the outcomes of all studies.

Assessment of Methodological Quality of Studies

The methodological attributes of the studies that were finally included in this review were evaluated using the PEDro scale, in order to identify the internal validity and the existence of sufficient statistical information in each study. This tool indicates the risk of bias in human subject research at different steps, such as the level of blindness, the between-group statistical comparability or the provided point measures and measures of variability. This data is analyzed in Table 2.

RESULTS

Our initial search of the PubMED database identified 68 articles, as shown in the PRISMA flowchart in Fig. 1, of which 61 remained after duplicates were excluded. Two articles reported results on EEG after applying Photobiomodulation on the palm instead of transcranial appliance and were excluded. Seven studies were conducted on healthy participants, one on adults with dementia diagnosis and one on adults at risk for cognitive decline in general (self-reported memory complaint, mild TBI history or mild cognitive decline diagnosis).

Vargas et al., [14] tried to investigate if there is an improvement in cognitive performance in adults who are at risk for cognitive decline, using EEG recording before, during and after transcranial infrared laser stimulation (TILS) on the right prefrontal cortex, applying coherent infrared light of a specific wavelength (1064 nm). The duration of the treatment was 8 mins and the laser session was administered once weekly, for 5 weeks. They concluded that there was an increase in alpha, beta and gamma oscillations, both ipsilateral to the stimulation side, as well as contralateral. Also, these alterations were observed not only during the laser stimulation but also after it (10 mins of EEG recording) and the increase was more obvious in occipital recordings, smaller in the parietal and frontal recordings, while for beta and gamma bands, the effect was more prominent in the temporal recordings.

Berman et al., [20] recruited 11 patients diagnosed with dementia and applied t-PBM using 15 arrays of LEDs all over the scalp, at 1060-1080nm, pulsed at 10Hz. There were 6mins sessions daily, for 28 days. The results showed improved EEG amplitude and connectivity measures.

Grover et al.,[21] conducted research with 31 participants who were healthy volunteers. They underwent qEEG event-related response tests before and after a 20-min Photobiomodulation session, using a cap with 784 NIR LEDs. This cap was covering occipital, left temporal, right temporal, frontal, and parietal lobes. Also, two to four months later, 18 participants returned, and there was another EEG measurement, with a 20-min rest period instead of the NIR light treatment. The results indicated an acute improvement of the reaction time and amplitude.

Jahan et al.,[15] recruited 30 healthy participants who underwent qEEG before and after a 10 mins PBM session of 850nm on the right prefrontal cortex and reported a reduction of the whole cortical delta band.

In Zomorrodi et al.,[18] research protocol, 20 mins of Photobiomodulation (810nm, 10Hz) was administered on 20 healthy participants and recorded 10 mins of rest EEG before and after the treatment. In their results there was an increase in all frequency bands for both active and sham group, which led them to conclude that resting wakefulness may increase cortical activation in general. Furthermore, active stimulation induced further and frequency-dependent increase in power in the higher frequency bands (alpha, beta and gamma) and suppression of the increase in the lower frequency bands (delta and theta).

Wang et al.,[16] applied 1064nm Photobiomodulation at the right prefrontal cortex of 20 healthy participants and used EEG recording before, during and after 11 mins of stimulation (recovery EEG recording time was 3 mins). They noticed significant increases of EEG spectral powers at the alpha and beta bands, notable at a "front-to-back" pattern, as well as the fact that this increase was progressive and reached its highest point during 8^{th} – 10^{th} min of stimulation. They concluded that the impact of photobiomodulation on EEG was frequency-dependent, time-dependent and location-dependent.

Vincenza et al.,[19] compared continuous light PBM not only to sham treatment but also to pulsed light PBM treatment. They recruited 10 healthy participants and recorded 5 mins EEG with eyes opened and 5 mins EEG with eyes closed, before during and after each 20-minute PBM treatment. They noticed a significant increase in high frequency bands (beta and gamma) after continuous light stimulation, which was reported over broad frontal – temporal regions. Nevertheless, this impact that was observed disappeared when pulsed light was administered, a phenomenon that was imputed by the authors possibly to the low total energy that was delivered.

Wang et al.,[17] investigated the hypothesis that Photobiomodulation and thermal stimulation induced distinct alterations of EEG. They administered 8 mins of PBM at 1064nm or thermal stimulation with temperature of 33-41°C and recorded eyes-closed EEG before, during and after the sessions, on a total of 57 healthy humans. They noticed that tPBM, in comparison to sham light stimulation, significantly increased alpha and beta oscillation power, whereas thermo-stimulation had the opposite effects on EEG. As far as the comparison between the real tPBM treatment and thermo-stimulation is concerned, tPBM induced a 30% increase for the alpha band in anterior and posterior regions and beta bands in a central-posterior pattern, as opposed to thermo-stimulation.

On the other hand, Ghaderi et al.,[22] tried additional different methodological approaches, such as spectral graph theory and Shannon entropy, in order to throw light on the dynamic effects of tPBM on brain networks. They administered only 2,5 mins of PBM over the right medial frontal pole and recorded EEG pre- and post- PBM session, for 5 mins each time. As far as the topology of brain networks is concerned, they noticed reduced centrality of the right hemisphere, which may be associated to the improvement in emotion and cognition, that has clinically been observed after PBM sessions. They also reported an increase of centrality of central electrode (Cz), that indicates increased information transfer between hemispheres. As far as the dynamical parameters are concerned, Ghaderi et al.,[22] noticed a reduction of the stability of synchronizability, which may be related to the fact that only one single region of the brain was light stimulated in their protocol (considering this as an inhomogeneous interruption) and an increase of the complexity of resting state networks, that positive effects of tPBM in human cognition can be attributed to.

DISCUSSION

Overall, it is observed that transcranial Photobiomodulation can cause an increase in high frequency bands and a decrease or suppression of increase of the lower frequency bands. This effect seems to have a frequency-dependent, time-dependent and location-dependent pattern, as it becomes more obvious after the 8th minute of tPBM and it develops from the frontal regions to the posterior ones (front-to-back pattern).

It is known that higher delta activation in an awake state is related to pathological conditions, such as cognitive impairment, Alzheimer's disease, brain tissue damage, anxiety, depression or even developmental or organic disorders. Also, in brain hypoxic conditions, where the focal blood flow is restrained, such as ischemic stroke or hypoxia, there has been evidence that the generation of slow waves is increased. More specifically, it seems that delta oscillation has an inverse correlation with the oxygen saturation and metabolism of the prefrontal cortex. The increased energy production and the higher concentration of NO which causes vasodilation and improvement of the cerebral blood flow affect basic cortical generators of delta waves, which are located mainly in the medial prefrontal cortex, anterior cingulate and the orbitofrontal cortex.

As far as the alpha oscillations are concerned, it has been shown that alpha waves play an important role in the integration and communication among different brain rhythms during brain activity and their enhancement might be attributed to the targeting of DMN, which has a dominant mechanistic role in the alpha generation process. Default Mode Network is a group of strongly connected regions of the brain such as posterior cingulate cortex, inferior parietal cortex, medial prefrontal cortex and medial temporal cortex that is activated when the subject is in resting state (task-free state). Malfunctions or disconnection of this system of neurons can lead to inability of the brain to stay in normal resting state. The noticed increase of power density as recorded in EEG in these regions (anterior frontal regions) may be the underlying mechanism of strengthening of neural function that PBM causes clinically.

Furthermore, most prominently, it seems that light can cause an increase in beta bands, which are related to somatosensory and motor functions, increased visual attention and cognitive stimulation. It is proposed that the tPBM-induced cognitive improvement might be explained by the ability of PBM to modulate and synchronize alpha and beta oscillations.

CONCLUSION

Near-infrared light thrown on the human brain seems to be able to modulate neuronal activity, through the enhancement of high frequency oscillations and the interception of the lower frequency ones. These findings may offer a possible explanation of the improvement of human performance on cognitive tasks that is shown in recent clinical trials. Further research is needed in order to clarify the exact impact of the different light parameters on human brain oscillations and the usefulness of that impact on various neurological conditions.

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ANNEX

Figure 1. Mechanism of Photobiomodulation Therapy in mitochondria[23]

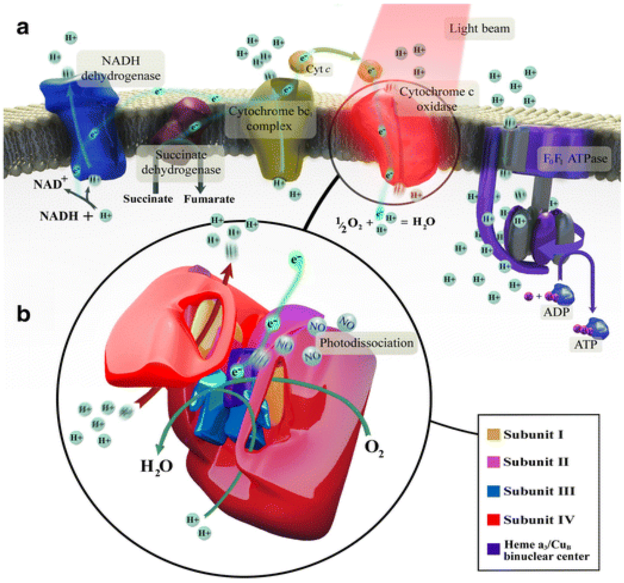

Figure 2. Neuro Gamma device, Vielight

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Figure 3. PRISMA flowchart for systematic review

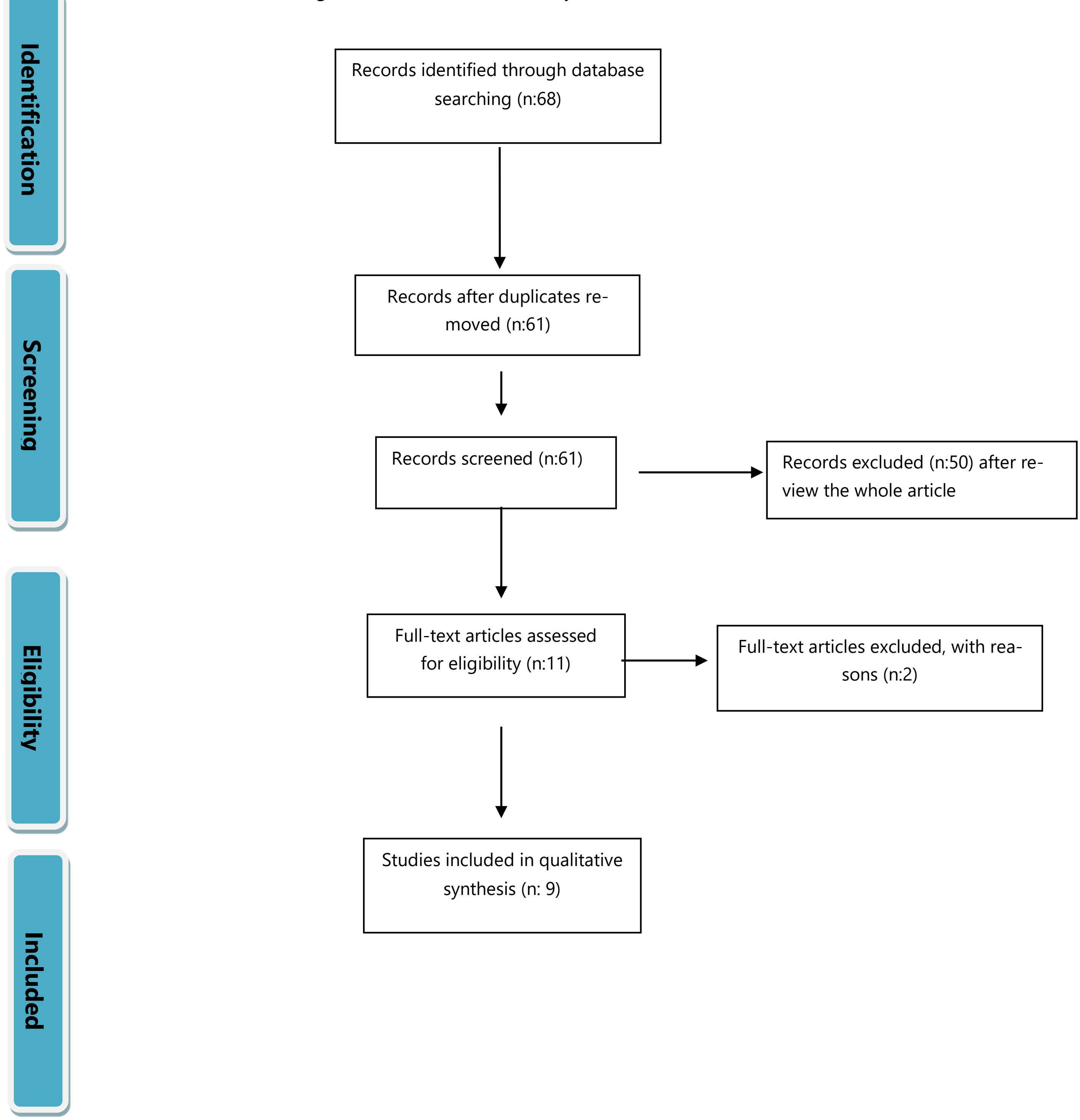

Table 1. PICOs criteria

Summary of studies on the effects of transcranial LED/laser light on human EEG according to **PICOs**				
Study/Year	Source/ Wavelenghts	Population	Irradiation parameters	Results (of real laser/LED treatment)
Vargas et al 2017	Right PFC, 1064nm	6 subjects with self-reported subjective memory complaint	Continuous laser wave power output 3.4 W power density 250mW/cm^2 Total energy dose per session 137,5J/ cm^2 Irradiation's duration 8 mins/session once per week, for 5 weeks	increases resting-state EEG alpha, beta and gamma power
Berman et al 2017	1100 LEDs set in 15 arrays all over head, 1060-1080nm	11 subjects with dementia diagnosis	Pulsed at 10 Hz Irradiation's duration 6 mins daily, for 28 consecutive days	Improved EEG amplitude and connectivity measures
Grover et al 2017	784 NIR LEDs covering all lobes, 903nm	31 healthy subjects 16-65 years old	Total dose of 20J/cm 2 Power density 16,67mW/cm^2 Irradiation's duration 1 session -20mins	Amplitude improvements in certain subjects (displaying initially low-voltage readings)
Jahan et al 2019	20 NIR LEDs - Right PFC, 850nm	30 healthy young adults 18-25 years old	Total power: 400nW Power density: 285mW/cm^2 Total dose (energy density): 60J/cm^2 Irradiation's duration 1 session - 2,5 mins	Significantly reduced delta band in all electrodes Significant interaction of group x time x frequency
Zomorrodi et al 2019	Positioned over the hubs of the DMN, 810nm	20 healthy adults 61-74 years old	Transcranial (and Intranasal) pulsed at 40Hz Total energy density: 240J/cm^2 Irradiation's duration 1 session – 20 mins	Suppression of the increase in the lower frequency bands Further increase in power in the higher frequency bands
Wang et al 2019	Right PFC, 1064nm	20 healthy young adults average age 26.8 +/- 8.8 years	Continuous wave laser, Laser Power:2,2W, Power density: 0.162W/cm^2, Energy density:107J/cm^2, Total energy dose 1452J Irradiation's duration 1 session – 11 mins	Significant increases of EEG spectral powers of alpha and beta bands (at broad scalp regions) Frequency-dependent, time-dependent, location dependent increases

Spera et al 2021	Four LED clusters, Frontal poles and dorsolateral PFC, 830nm	10 healthy subjects 20-56 years old	Power density:54.8mW/cm^2 Continuous wave: total energy 2.3KJ, average fluence 65,8J/cm^2 Pulsed light: 10Hz, total energy:0.8KJ, average fluence 21,7J/cm^2 Irradiation's duration 1 session – 20 mins	c-tPBM: Significant increase in the hidh frequency bands (beta and gamma) Most of these effects disappeared when pulsed light was delivered
Wang et al 2021	Right PFC, 1064nm	49 healthy subjects average age 26 +/- 8.8 years	Continuous wave Total power:3.5W, Power density 0.25W/cm^2 Total energy dose 1680J Irradiation's duration 1 session – 8 mins	Significant increase of alpha and beta bands
Ghaderi et al 2021	20 NIR LEDs - Right medial frontal pole, 850nm	40 healthy young subjects average age 21.31 (SD 2.21) for sham and 21.21 (SD 2.57) for real PBM	c-tPBM Total power: 400Mw Power density: 285mW/cm^2 Total dose: 60J, Energy density:42,75J/cm^2 Irradiation's duration 1 session – 2,5 mins	tPBM can alter topology of resting state brain network to facilitate the neural information processing, reduce stability of synchronizability and increase complexity in the resting state brain networks
PFC: Prefrontal Cortex, NIR: Near-infrared, LED: Light-Emitting Diode, DMN: Default Mode Network, EEG: Electroencephalogram, c-tPBM: continuous-light transcranial Photobiomodulation				

Table 2. PEDro scale

PEDro scale									
	Vargas et al 2017	Berman et al 2017	Groover et al 2017	Jahan et al 2019	Zomorrodi et al 2019	Wang et al 2019	Vincenza et al 2021	Wang et al 2021	Ghaderi et al 2021
Eligibitily criteria	yes	yes	yes	no	no	no	yes	yes	yes
Random allocation	no	yes	no	yes	yes	no	no	no	yes
Concealed allocation	no	no	no	no	no	no	no	no	no
Baseline comparability	yes	yes	yes	yes	yes	yes	yes	yes	yes
Blinded subjects	no	yes	no	no	yes	yes	yes	yes	no
Blinded therapists	no	yes	no	no	yes	no	no	no	no
Blinded assessors	no	no	no	no	no	no	no	no	no
Follow-up	yes	no	yes	yes	yes	yes	yes	yes	yes
Intention to treat	no	no	no	no	no	no	no	no	no
Between-group statistical comparisons	yes	yes	yes	yes	yes	yes	yes	yes	yes
Point measures and measures of variability	yes	yes	yes	no	yes	no	yes	no	yes
Score	4	6	4	4	7	4	5	4	5