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Review Article

Psychiatry Section

Non Pharmacological Cognitive Enhancers – Current Perspectives

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ABSTRACT

Cognition refers to the mental processes involved in thinking, knowing, remembering, judging, and problem solving. Cognitive dysfunctions are an integral part of neuropsychiatric disorders as well as in healthy ageing. Cognitive Enhancers are molecules that help improve aspects of cognition like memory, intelligence, motivation, attention and concentration. Recently, Non Pharmacological Cognitive Enhancers have gained popularity as effective and safe alternative to various established drugs. Many of these Non Pharmacological Cognitive Enhancers seem to be more efficacious compared to currently available Pharmacological Cognitive Enhancers. This review describes and summarizes evidence on various Non Pharmacological Cognitive Enhancers such as physical exercise, sleep, meditation and yoga, spirituality, nutrients, computer training, brain stimulation, and music. We also discuss their role in ageing and different neuro-psychiatric disorders, and current status of Cochrane database recommendations. We searched the Pubmed database for the articles and reviews having the terms 'non pharmacological and cognitive' in the title, published from 2000 till 2014. A total of 11 results displayed, out of which 10 were relevant to the review. These were selected and reviewed. Appropriate cross-references within the articles along with Cochrane reviews were also considered and studied.

Keywords: Ageing, Cognitive impairment, Dementia,Neuro-psychiatric disorders

INTRODUCTION

Cognition refers to the higher mental functions of the brain and includes thinking, language, memory, attention, perception, planning, intelligence and problem solving [1]. They are subjective in nature and may be affected by number of factors including ageing, stress, various medical conditions such as hypertension, dementias, Parkinson's disease (PD) and psychiatric illnesses like schizophrenia, bipolar disorders [2,3]. All these disorders have some components of or predispose to cognitive decline or dysfunction.

Cognitive dysfunction is the decline in intellectual functions such as thinking, reasoning and remembering, which interferes with daily functioning. Considering the ever increasing population of the elderly and stress related problems, cognitive decline is an epidemic in the making [4]. Thus, memory enhancers are predicted to play a great role in the near future. Cognitive Enhancers (CE) are molecules (drugs, supplements, nutraceuticals, and functional foods) or various brain stimulation methods that improve some aspect of brain function or cognition [5]. They may be Pharmacological Cognitive Enhancers (PCE) or Non-Pharmacological Cognitive Enhancers (NPCE). PCE include herbal medicines (asparagus, gingko biloba, and ginseng) and pharmaceutical drugs. Only a few PCE are approved for enhancing cognition, most do not have established efficacy, have out of label use or are under research. Also, the ethical issues of using PCE in healthy ageing subjects are of great concern. These concerns have promoted the use and research for NPCE.

NPCE include physical exercise, sleep, meditation, computer training, brain stimulation, yoga and music. These are largely ignored and neglected, despite being relatively safe and culturally accepted. Cochrane Reviews on non-pharmacological interventions have found relative paucity of evidence regarding the effects of these interventions. This review describes various NPCE, the role of NPCE in ageing and various neuro-psychiatric disorders, and the current status of Cochrane database recommendations. We searched the Pubmed database for all articles and reviews having the terms 'non pharmacological and cognitive' in the title, published till 2014 since the year 2000. A total of 11 results displayed, out of which 10 were relevant to the review. Appropriate cross-references within the articles were also considered and studied. Cochrane review database was searched for the terms 'exercise', 'sleep', 'yoga', 'computer training', and 'music therapy'. Appropriate results pertinent to review were selected.

A range of strategies from environmental stimulation to exercise have been tested and developed to enhance cognition. Most interventions target either underlying disease pathologies or the processes underlying normal cognition.

PHYSICAL EXERCISE

Physical exercises, especially aerobic exercises, are documented to enhance and preserve cognitive functions. Hillman suggested that regular aerobic exercises improve cognition and have beneficial effects on brain functions [6]. Exercise is thought to enhance production and release of neurotrophins specially, brain-derived neurotrophic factor (BDNF) and also induces a cascade of molecular and cellular processes that favor angiogenesis, neurogenesis and synaptogenesis [7]. Physical activity is also hypothesized to improve mood and cognition by increasing the synaptic transmission of monoamines as well as enhancing the release of endorphins.

The effect of exercise has been studied across different age groups. Physical exercise was demonstrated to benefit intelligence and academic functions in school age children [8] as well as improve different aspects of cognition in older adults with and without pathological cognitive decline [9]. A recent meta-analysis [10] demonstrated that aerobic exercise improves cognitive functions such as memory, processing speed, attention, and executive functions. It may be concluded that physical activity helps to preserve mental abilities throughout aging and across all age groups.

Exercise also benefits subjects suffering from Mild Cognitive Impairment (MCI) or early-stage dementia [10]. Evidence suggests that exercising in young leads to better cognitive output in elderly and it follows dose-response effect [11]. The prefrontal and medial temporal cortices, particularly hippocampus, are sensitive to exercise with trophic responses leading to increased volume and

increases in hippocampal cerebral blood flow [12]. Exercise is considered protective for Alzheimer's Disease. Several studies have reported reduced incidence of dementia or cognitive deterioration with physical activity [13]. Daily physical training of 30 minutes reduces the number of hospitalizations in AD patients [14]. Exercise is considered as an adjunctive treatment and a preventive measure in Parkinson's Disease (PD). Specific core areas for physical exercise therapy in PD includes cueing strategies to improve gait, cognitive movement strategies to improve transfers, special exercises to improve balance and training of joint mobility and muscle power in order to improve physical capacity [15].

Patients with serious mental illnesses may also benefit with exercise. Exercise has been shown to effectively treat depression and anxiety disorders along with enhancing cognition [16,17]. Physical exercise is an important component of stress reduction programs and has shown on psychological well-being [18]. Exercise also improves symptoms such as reduced self esteem and social withdrawal. A cochrane systematic review found exercise to significantly improve negative symptoms of mental state along with quality of life [19]. No effect on positive symptoms was noted. However, one recent review found that exercise programs had no significant effect on symptoms of mental health [20]. We can conclude that there is converging evidence on several levels that physical exercise benefits and preserves cognition throughout the lifespan and across various neuropsychiatric disorders.

SLEEP

Sleep is considered important for effective functioning of brain and cognition. Researchers have suggested that wide variety of cognitive functions ranging from attention and memory, to language and reasoning, are affected due to lack of adequate sleep [21]. Sleep-specific manipulations have been found to effectively enhance cognitive functions [22].

Sleep facilitates several cognitive functions such as working memory, language processing, creativity and decision making [23]. Short periods of day time naps benefit memory performance and concentration, even in subjects who are not sleep deprived. Sleep facilitates memory consolidation as well as subsequent acquisition of new learning material [23]. Sleep also promotes the integration and reprocessing of fresh memories into the existing reservoir of long-term memories [24].

Surprisingly, inspite of so much research on sleep and its role in memory enhancement, it is usually neglected in therapeutic aspects. The sleep state might be particularly well suited as a target for the enhancement of memory capacities. First, sleep can be timed in relation to learning so that it optimally supports encoding and memory consolidation. This may be possible by introducing short naps before learning of new information [25]. The second way to augment memory during sleep is to manipulate memory and/or sleep directly in such a selective way that it targets the processing of specific memory functions during sleep [22]. Pharmacological agents can also be used to modulate the processing of memories during sleep. However, new learning of declarative and procedural memories during sleep is still out of question [22].

One of the clinical applications of sleep may be in restoring normal cognitive functioning. Many neuro psychiatric and degenerative disorders are accompanied by changes in sleep patterns and dysfunctions of memory. Memory for words improved in patients with schizophrenia following stimulation of slow oscillations with transcranial direct stimulation during sleep [26]. However, it was observed that administration of olanzapine (which increases slow wave sleep), and GABA agonist eszopiclone, failed to normalize memory consolidation in schizophrenia patients [27,28]. This calls for further research to clarify and establish the role of sleep for enhancing cognition in these patients. In the treatment of spider phobia, increase therapeutic effectiveness was found if exposure therapy was followed by sleep [29]. A study found sleep problems to be associated with cognitive errors seen in anxiety and depression [30]. Depressed patients treated with olanzapine showed improvement in sleep quality and it correlated with improvement in cognition and illness severity [31].

Sleep disturbances appear even before cognitive symptoms in the preclinical phase of AD. Poor quality sleep has been linked with greater cognitive decline and increased risk of mild cognitive impairment and dementia. Cognition declines faster in older adults who have disturbed sleep than those who sleep well [32]. Lee et al., concluded that patients with ADHD have more sleep problems compared with controls, which positively correlated with the cognitive functions [33]. In conclusion, sleep enhances some aspects of cognition but future research is needed to establish its role as a cognitive enhancer and to evaluate the timeframe for which the benefits persist.

MEDITATION AND YOGA

Meditation has been emphasized to promote mental well-being, enhance attention and other cognitive capacities. Traditional approaches like Buddhist mindfulness meditations and Zen meditations have resurged along with several modern group-based standardized meditations. Meditation practice has been associated with increased attention performance and cognitive flexibility in experienced meditators as compared to control subjects [34].

A systematic review found preliminary positive effects of meditation on attention, memory, executive function, processing speed, and general cognition in age related cognitive decline and degenerative disorders [35]. Cochrane database review found no significant benefits of meditation therapy in children or adults diagnosed with ADHD [36]. Another cochrane database review found that transcendental meditation is comparable and as effective in reducing anxiety as other relaxation therapies [37]. Mind fulness interventions have been found moderately effective in treating negative symptoms in Schizophrenia and can be useful adjunct to pharmacotherapy [38].

Yoga has its origins in Indian culture and is the oldest known form of meditation. Yoga based interventions appear to significantly improve several cognitive domains in elderly such as immediate and delayed recall, verbal and visual memory, attention, working memory, verbal fluency, executive function and processing speed [39]. Yoga has emerged as an effective and feasible add on therapy in schizophrenia, with special benefits in improving social cognition and negative symptoms [40]. However, a review comparing yoga to exercise found no short term evidence of effects on positive symptoms, negative symptoms, quality of life and social function [41]. Yoga was found to benefit individuals with depressive symptoms, including quality of life and cognition [42]. Some of the consistent effects of yoga practice include stress reduction, emotion regulation, improved mood and well being. It can be concluded that yoga and meditation are safe and effective traditional methods for enhancing cognition and their use should be encouraged. Considering the multiple benefits of Yoga, the World Health Organization has declared 21st June as the 'International Yoga Day' [43].

SPIRITUALITY

Spirituality is considered as an important component of overall well-being. Spirituality helps an individual cope with stressors in the world and strives towards his potential. Inspite of growing recognition of religion and spirituality as part of the treatment/rehabilitation plan for cognitively impaired patients, there are limited studies that focus on its role for enhancing cognition.

Studies suggest that a few aspects of spirituality may assist in decreasing depressive symptoms, including cognitive errors [44]. Evidence shows that religious beliefs and spirituality may lead to enhanced levels of psychological well being, coping capacities,

fewer symptoms of distress, depression, anxiety and more positive affect [45]. Individuals with strong religious convictions often utilize positive religious coping behaviours to assist with stress reduction and emotion regulation. Kaufman et al., [46] found that spirituality and religious practices, such as prayer, Bible reading, and devotions, may decrease the rate of cognitive decline of Alzheimer's patients. Religion and spirituality benefit participants in psychosocial rehabilitation programs.

In general, spirituality strengthens a sense of self and self-esteem and helps in countering stigma and shame with positive self-attributions [47]. Higher spiritual inclination are found to have positive effects for persons diagnosed with Schizophrenia [48] and are associated with optimism and resiliency against stress among individuals recovering from substance abuse [49]. Spirituality empowers confidence, presents a sense of purpose and opportunities for growth and positive change.

However, spirituality in itself is not free of negative consequences. Negative religious coping activities such as expressing anger at God, attributing negative events to God's punishment has been linked to greater affective distress, including greater anxiety, depression, suicidality and lower self-esteem. Furthermore, emotional struggles and feelings of rejection can be reinforced by religious communities who see mental disorders as signs of moral or spiritual failure. Hence, caution needs to be taken while using spirituality in neuropsychiatric disorders and enhancing cognition.

MUSIC

Music has been recently emphasized as an alternative way of enhancing cognition. Music therapy and other musical activities like listening to music, singing and playing a musical instrument have shown promise in neuropsychiatric disorders, especially in dementia.

Two main types of music therapy are described: receptive and active music therapy. "Receptive music therapy consists of listening to music by the therapist who sings or selects recorded music for the recipients. In active music therapy, recipients are actively involved in the music-making and playing instruments. The participants are encouraged to participate and improvise with instruments or voice, and with dance, music or singing" [50].

In Alzheimer's patients, music part of memory seems interestingly spared by the disease [51]. Elderly adults who frequently play a musical instrument are less likely to develop dementia. Positive effects on scores on working memory, perceptual speed, and motor skills were noted in elderly population after piano lessons [52]. Music, amongst other cognitive exercises like puzzles and crosswords, was proposed to have the strongest neuro-protective effect [52]. A study showed the effectiveness of group music therapy on depression and cognitive functions, particularly short term recall function among elderly persons with mild and moderate dementia [53]. Choir music was found to reduce depression, increase levels of motivation, purpose, wellbeing and quality of life in people with dementia [54].

Music therapy may have a role in psychosocial rehabilitation in enduring mental illnesses. It helps improve an individual's psychological and physiological well-being, social cohesiveness and emotional expressions [55]. It helps in reducing social isolation, and improves participation in external events. Music therapy significantly improved aggression/hostility in pre adolescents with emotional, learning, and behavioural problems. A randomized trial of music therapy for in patients with Schizophrenia found benefits in negative and cognitive domains but not so in positive symptoms [55]. Gold et al., concluded that music therapy sessions help improve mental state and global functioning in Schizophrenia. Therefore, it adds to the standard care of treatment [56]. A Cochrane review suggested that music therapy improves mood, is accepted by people with depression and acts as a protective factor in clients with suicidal ideation [57]. We can conclude that initial results of including music in cognitive training are encouraging. However, quantitative research based evidence is lacking in this field.

COGNITIVE TRAINING

Techniques of stimulating brain and cognition are widely practiced in areas of sports and rehabilitation. There have been studies and debates about different types of techniques involved in cognitive enhancement in ageing population, dementia and neuropsychiatric disorders.

Visualization techniques require users to vividly imagine themselves performing a task (running a race, going to a store), repeatedly imagining every movement and the associated feelings [58]. These exercises are hypothesized to work by activating the neural networks which are involved in skill execution simultaneously as the task is held, optimizing neural reorganization.

The concept of enhancing working memory (WM) through targeted training has mounting evidence. Training related increase in WM capacity can improve a range of important cognitive skills. The training paradigms usually teach effective approaches to encode, register, and retrieve from WM [59]. Such methods of 'strategy training' have been successfully used in children with Down syndrome [60] to supplement specific WM deficits. Strategy training was reported to slow the decline of, and perhaps improve, WM in older adult populations [61]. Self-report measures indicating improved everyday memory in trained older adults suggest utility of this training module. 'Core training methods' are designed to target 'domain-general WM mechanisms'. These involve repetition of cognitively stimulating high intensity WM tasks, which improves WM [59]. Core training programme found benefits in cognition and intelligence in young healthy adults, in cohort of children diagnosed with ADHD [62], quality of life improvements in patients with multiple sclerosis [63], and patients with stroke and Schizophrenia patients [64].

Memory therapy in the mild to moderate stages of AD can be successful, provided it is individualized based on patient's daily problems and their residual cognitive capacities. Cognitive training is an efficient method to delay cognitive decline in persons with MCI. Some techniques of cognitive stimulation make use of ecological or virtual environments to compensate age related cognitive decline. Several types of cognitive trainings are available aimed at improving memory, learning, attention, executive functions, mnemonic techniques, or global cognition [65].

Mnemonic strategies can be seen as strong and reliable enhancers of learning and memory capacity. The ability to cope with verbal or numerical information becomes increasingly important and complex as age progresses. Mnemonics have been shown to be effective for retaining easy-to-learn material with small effect sizes. For difficult tasks, effect sizes may be as high as Cohen's d of 3 or 4. But mnemonics have not proved effective in age-related cognitive decline [66].

Cognitive Remediation therapy (CRT) aims to improve cognitive processes in dementias and neuropsychiatric disorders. CRT expects that changes will maintain over follow up period and will translate into real world benefit. A meta analysis of cognitive remediation in Schizophrenia by McGurk et al., found that CRT resulted in significant improvements in most domains of cognition [67]. Cognitive adaptation training is a structured program that utilizes measures such as mobile phone reminders and medication administration aids that help with daily functioning [68]. Similarly, social cognition remediation programs have been developed especially in regard to improving emotional perception, and facial affect recognition.

BRAIN STIMULATION

Brain stimulation techniques were developed for therapeutic purposes in psychiatry or neurology. They act by influencing regions of the brain non-specifically rather than by some physiological alterations. Some of these methods are non invasive, while other achieves greater selectivity by placing electrodes inside or on the brain. Non invasive techniques include Transcranial Direct Current Stimulation (tDCS) and Transcranial Magnetic Stimulation (TMS). Invasive methods include Deep Brain Stimulation (DBS) and direct vagus nerve stimulation (dVNS). Some of these techniques exhibited cognition enhancing effects on healthy individuals [69].

While most of these methods help in encoding of memory and learning, a few like DBS may directly modulate and affect memory systems [70]. tDCS and TMS are the most researched. Anterior temporal lobe tDCS and paired pulse TMS stimulation during encoding help enhance speed of recall [71,72]. Studies have found tDCS to enhance performance on working memory tasks, learning and recall of words on stimulation of left dorso-lateral prefrontal cortex (DLPFC) during encoding [73]. TMS and tDCS have been found to enhance procedural skills by influencing brain plasticity and learning motor tasks by stimulation of the motor areas useful in rehabilitation and therapy. fMRI guided studies have shown stimulation of the right cortical region to be most successful. The most common side effects reported are headaches, local pain and confusion. The most serious risk is the occurrence of seizure.

There is limited data on cognitive restoration or enhancement in neuropsychiatric disorders. Efficacy of rTMS on cognitive performance in depressed individuals has yielded mixed results. Among 13 trials comparing active and sham rTMS, 8 did not report significant differences in regards to cognitive functions [74]. However, some studies did report improvement in cognitive functions after rTMS over the left DLPFC. Many studies found benefits in psychomotor speed and concentration, mood, executive functions and visuospatial ability, procedural learning, verbal learning, working memory and language in depressive disorders, post stroke depression and depression with PD [75,76]. tDCS in depression has also shown cognitive improvements in different domains [77]. Significant effect of rTMS in cognitive functions in schizophrenia has been observed [78]. However, one study did not find any cognitive improvement [79]. Ahmed et al., found significant improvement in global cognitive functioning by rTMS applied over the bilateral DLPFCs in Alzheimer dementia [80] which was replicated in other RCTs [74]. In ADHD, a recent cross over study found beneficial effects of right DLPFC rTMS in attention [81]. rTMS has been proposed as a potential tool that may improve the symptoms of autism spectrum disorders, specially error monitoring and post-error response correction [82]. We can conclude that these methods have beneficial effects on cognitive enhancement, although extensive research is needed to evaluate long term benefits.

COMPUTER BASED INTERVENTIONS

The rapid popularity and the concept of internet gaming addiction in adolescents have generated concern among practitioners and policy makers. However, Computer based repetitive stimulation allows training of various cognitive tasks, which promotes cognitive well being. Computer based training programs have shown improvements of memory, attention, executive function and processing speed along with working memory and episodic memory in young and older adults [83]. There has been focus on enhancing long term memory or brain plasticity to prevent dementia and age related cognitive decline [84]. There have been variable effect sizes of computerized training on the cognitive domains. Processing speed and perceptual measures show medium to large effect sizes, while memory domains are only in the small or medium range [83]. It has been shown that improved cognitive performances maintained for 6 months after suspension of training, supporting the idea that age-related decline cannot be only halted, but actually reversed. However, Whitlock et al., reported no effects of game-based cognitive training on visuo spatial navigational abilities and memory [85]. Moreover, increased aggression and reduction of empathy have been reported for violent computer games [86].

Intensive, computer based cognitive training has showed improvement in verbal learning and memory in MCI subjects [87]. A cognition-specific computer based cognitive training program in PD patients found improvement in attention and memory [88]. Cognitive remediation therapy, delivered via computerized programs, of varying length and complexity has been found effective in people with severe, chronic mental illnesses such as Schizophrenia, bipolar disorders and depression. Still, better study designs are needed to develop and individualize computer based therapies for different neuropsychiatric disorders.

CONCLUSION AND FUTURE RESEARCH

We summarized the effects of non pharmacological interventions on cognition in healthy individuals, ageing population as well as in neuropsychiatric disorders. All the non pharmacological interventions can be envisioned to be somewhat effective in maintaining and perhaps improving optimal levels of cognitive capabilities. Some of the NPCE such as sleep, meditation, exercise, music, spirituality, are based on widely accepted traditional habits. Others like, brain stimulation, cognitive training and computer based interventions are modern and complex.

Most of these are cost effective and relatively free of adverse effects. Still, many issues are unresolved and need clarification. The most important is of ethical concerns. Voices have been raised on possible issues of doctors “playing Gods” by trying to enhance what is inherited, interference in nature, autonomy of patients, selective improvements in cognitive domains, and improper use of NPCE for competition in today’s world.

These methods are still evolving and need strong research based evidence before being conclusively used in clinical setting. They may well be used as adjuvant therapeutic tools in the early stage of neurodegenerative conditions. Comparative research on the variety of currently existing NPCE is strongly needed to evaluate the similarities and differences amongst them, so as to individualize the therapy based on specific cognitive profile of the patient.

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