Cognitive enhancement: toward the integration of theory and practice

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Introduction

As a species, humans have always relied on their adaptability and intelligence in order to survive. It seems that all humans, regardless of their country, culture or race, have a natural tendency to always grow, develop, and learn. Because of this, there has always been great interest in how to grow, develop, and learn even more. This has been one of the most important drives for the field of cognitive enhancement. Cognitive enhancement is the use of any means (e.g., brain stimulation, video-gaming, food supplements) aimed at enhancing cognitive performance (e.g. creativity, memory, etc.) in healthy individuals. Cognitive enhancement has gained great attention over the past years, as the economic problems of the welfare system (i.e., increasing costs) have boosted the interest in procedures and activities that make welfare more affordable for society. That is, from an economical point of view, cognitive enhancement may help to decrease the costs of the welfare system. Especially with regard to the aging population, cognitive enhancement techniques may be used to delay cognitive decline in the elderly, which would extend the time people can live autonomously and, as such, reduce welfare costs. Similarly, the risk of behavioral problems and pathology in children can be reduced by training them – which likewise implies considerable decreases in the costs of our welfare systems. Enhancing cognitive functions may also speed up their education, which benefits society's educational systems.

In addition to the economic benefits that cognitive enhancement may bring, there is another viewpoint from which cognitive enhancement is gaining interest. That is, Western societies seem to continuously be driven towards more individualism, which emphasizes the existence and importance of individual differences. This includes the view of the individual as a director of his or her own life and a rather systematic deconstruction of the collective welfare system. This ideological turn towards individualism offers a natural breeding ground for a growing public interest in procedures and activities that help to express individual needs as well as to minimize weaknesses and further support strengths. As a result of this ideological trend and the economical trend as described above, research on cognitive enhancement has benefited from a great increase in political, public and academic interest.

Need for theory

"*There is nothing so practical as a good theory*" – Kurt Lewin (quoted in Marrow, 1969)

Findings showing that individuals become better in a certain task after being stimulated, trained, or supplemented with one of the means of cognitive enhancement are meaningful from a practical point of view, although often not new. Many cognitive enhancement approaches do not go beyond concluding that the applied method has an enhancing effect. The typical problem that these approaches then run into is the inability to replicate the effect in related processes in subsequent studies, or to report any effect at all. One possible cause of this problem is that existing studies on cognitive enhancement have mainly been driven by practice (i.e., effect-driven), demonstrating enhancing effects of certain interventions. However, they often do not explain why cognitive enhancement should occur, or which mechanisms could have caused or modulated the effects. However, in order to reach interesting levels of enhancement, and in order to be able to apply this in other fields, clear ideas about the mechanisms underlying the cognitive functions one aims to improve are needed. That being said, it may be clear that Kurt Lewin's claim of nothing being as practical as a good theory applies nowhere better than in the field of cognitive enhancement, with practice being the observed effect and theory being the knowledge that explains the underlying mechanism(s). The present dissertation therefore aims to get a better understanding of the underlying mechanisms of how enhancing techniques affect cognition in healthy humans.

Overview

The means of cognitive enhancement involve various devices, drugs, and food supplements used to enhance cognitive functions. For example, brain stimulating devices targeting specific brain areas aimed at improving attention or working memory, or pills (e.g., methylphenidate) taken by students to help focus on their studies. As can be inferred from these two examples, cognitive enhancement is generally aimed at improving executive functioning including attentional control, inhibitory control, working memory, and cognitive flexibility, but can be aimed at improving social cognition as well. That is, social cognition and social behavior stem from numerous cognitive processes (e.g. attention), and can therefore be targeted by cognitive enhancement. In this thesis, enhancing effects on both cognitive and social functioning, and their underlying mechanisms are therefore discussed.

Brain stimulation

The stimulation of certain brain areas and/or the synthesis and release of certain neurotransmitters by applying electrical stimulation has been done for decades already. Techniques such as magnetic stimulation (TMS), transcranial direct current stimulation (tDCS), and vagus nerve stimulation (VNS), which use electrical stimulation have received considerable attention over the past years. In contrast to imaging techniques, which provide only correlational evidence, these techniques allow us to infer causal relations between the stimulated neurotransmitter system or brain area and the related cognitive function measured. In **Chapter one**, we introduce a technique called transcutaneous vagus nerve stimulation (tVNS) that, in contrast to direct vagus nerve stimulation (VNS), provides an easy, non-invasive and relatively safe method to stimulate the tenth cranial nerve (i.e., vagus nerve) in healthy subjects. This technique is applied by placing an electrode medial of the tragus at the entry of the acoustic meatus in the left ear. The electrode stimulates the afferent auricular branch of the vagus nerve by applying a weak electrical current through the skin. This technique provides a relatively safe and easy way to investigate the role of the gamma-aminobutyric acid (GABA)-ergic and noradrenergic systems in cognitive processes. In this chapter, we investigate the role of these two systems in action cascading processes. That is, the ever-changing environment we are living in requires us to apply different action control strategies in order to fulfill a task goal. Indeed, when confronted with multiple response options it is fundamental to prioritize and cascade different actions. So far, very little is known about the neuromodulation of action cascading, although there is evidence showing that the GABA-ergic system is important because of its inhibitory features. There is also evidence showing that stress modulates action cascading processes, and stress is known to affect the noradrenergic system. So there is tentative support for the idea that norepinephrine (NE), playing an important role in stress responses, may affect functions during action cascading and lead to slowing of responses during multitasking. Given the idea that GABA – the main inhibitory neurotransmitter - and NE impact action selection, it was expected that active tVNS would improve action cascading processes. That is, tVNS would decrease reaction times on trials where responses have to be inhibited and changed to an alternative response, both when a person has to stop and change to an alternative response simultaneously, and when a person has to change a response when the first action is already successfully inhibited. This hypothesis is further supported by the fact that, from an anatomical point of view, action cascading efficiency is related to a neural network that includes the anterior cingulate cortex (ACC). Indeed, functional magnetic resonance imaging (fMRI) studies have shown an increase in activity in the cingulate cortex during active tVNS. Importantly, the vagal nerve is connected to the ACC, and the ACC is a crucial area for the execution of multi-component behavior. In this chapter, we demonstrate that active tVNS indeed modulates action cascading efficiency, providing considerable support for the idea of a crucial role of the GABA-ergic and noradrenergic pathways in action cascading.

Besides affecting the GABA-ergic and noradrenergic systems, two recent functional magnetic resonance imaging studies showed increased activation in the thalamus, prefrontal cortex (PFC) and insula during active tVNS in healthy humans. Importantly, these areas are key areas related to social cognition such as social pain and mentalization (i.e., the ability to understand the mental state of oneself and others), and are linked to vicarious ostracism (i.e., the observation of other people being socially ignored and/or excluded). Interestingly, observing ostracism increases activity in the insula and ACC, areas that are also activated when directly experiencing ostracism. Moreover, observing ostracism activates the PFC and precuneus—brain regions associated with mentalization. Brain activation of both the mentalization areas and social pain-related regions correlates with individual differences in empathy when observing ostracism and with prosocial behavior toward the victim. This has been taken to suggest that differences in experiencing vicarious ostracism may also reflect individual differences in trait empathy. In **Chapter two** we assessed the causal role of this PFC-insula network in mediating vicarious ostracism and investigated whether active tVNS can modulate vicarious ostracism using an adapted version of the Cyberball game (Williams, 2009), a virtual ball-tossing game designed to measure prosocial compensation for ostracism. Given the available correlational evidence that vicarious ostracism involves the PFC-insula network, we hypothesized that tVNS would enhance prosocial helping behavior (i.e., increase the amount of ball-tosses to the ostracized person) in the Cyberball game. However, in this study we found that active tVNS did not increase prosocial helping behavior toward an ostracized person, as compared to sham (placebo) stimulation. Corroborated by Bayesian inference, which allows us to make inferences about non-significant effects by estimating the probability of their occurrence, we therefore conclude that tVNS does not modulate reactions to vicarious ostracism, as indexed by performance in a Cyberball game.

As described in the Introduction, cognitive enhancement and its methods have received considerable attention from the greater public. That is, the increased individualistic society stresses individual differences and encourages minimizing our weaknesses. Techniques such as tDCS, which has been shown to be effective in enhancing cognitive processes such as working memory, have therefore been brought on the market by what is called the ‘brain-training industry’. Commercial tDCS devices are supposed to have the same effects as medical tDCS devices, which are used to deliver a weak electrical current to the brain by placing two electrodes on the head. Depending on the placement of the electrode, neuronal activity under the ‘anodal’ electrode is supposedly increased, whereas that under the ‘cathodal’ electrode decreased. The electrical current delivered by the tDCS device depolarizes (anodal) or hyperpolarizes (cathodal) membrane potentials, as such causing a relative increase or decrease in spontaneous neuronal firing. Although the actual effectivity of tDCS in modulating cognitive functions remains topic of debate because of the various factors (e.g. stimulation parameters, individual differences like genetic predispositions and hair thickness, anatomical differences, experimental design, etc.) influencing the effectivity of tDCS, consumers are told that using the commercial tDCS devices or playing so-called ‘brain games’ will make them smarter, better able to focus, and quicker learners. In the long run, this is said to perhaps even reduce cognitive decline associated with aging, and improve everyday functioning and memory. However, a recent consensus signed by several prominent researchers calls for a more critical and active role of the scientific community in evaluating the sometimes far-reaching, sweeping claims from the brain training industry with regard to the impact of their products on cognitive performance. In **Chapter three** we investigated whether the commercial tDCS headset *foc.us* (V.1), can indeed improve working memory, as advertised in the media. We applied the commercial tDCS headset to healthy participants, who then received a low intensity current to the frontal part of the brain administered by electrodes. Either during or after the stimulation, we asked participants to perform a working memory task in which they had to update remembered information. Findings showed that, compared to when the participants received sham stimulation, active stimulation actually impaired working memory performance. Even if preliminary, we believe that these results show the importance of a critical and active role of the scientific community in evaluating the claims made by the brain-training industry. More specifically, given the potential risks of misusing tDCS, and the fact that its long-term effects on the brain have not yet been fully explored, we believe that there is a need for regulations or official guidelines for the commercial use of tDCS.

Cognitive training

Chapter four focuses on the idea that certain lifestyles can enhance cognitive abilities because they train certain cognitive functions in itself. In this chapter, we test the idea that action videogames (AVGs), especially first person shooter games, require gamers to develop different action control strategies to rapidly react to fast moving visual and auditory stimuli, and to flexibly adapt their behavior to the constantly changing context of the game, and that this generalizes to cognitive control abilities. It is expected that playing first person shooter videogames is associated with enhanced action cascading performance. Replicating previous findings, it was demonstrated that, compared to non-videogame players, videogame players showed higher efficiency in response execution, but similar performance with regard to response inhibition (i.e. inhibitory control). Videogame players showed enhanced action cascading processes both when an interruption (stop) and a change towards an alternative response were required simultaneously, as well as when such a change had to occur after the completion of the stop process. The findings in this chapter suggest that playing AVGs is associated with enhanced action cascading and multi-component behavior without affecting inhibitory control. The latter finding is particularly intriguing as it challenges the anecdotal idea that AVG players are more impulsive than non-videogame players. If this would indeed have been the case, AVG players would have shown lower inhibitory efficiency than non-videogame players – but this was not the case. These findings may therefore represent an important first step in stimulating further research to assess whether videogames can be used to optimize cognitive control. Importantly, given the importance of action control in daily activities and the known difficulties shown by older adults in response selection and action cascading processes, the findings can have important practical implications for designing intervention/training studies aimed at overcoming or slowing down action control deficits associated with aging. However, one of the drawbacks of this chapter with regard to the implications it has for the general public, at least for now, is that the AVG players that were shown to have enhanced action cascading efficiently played first person shooter videogames for at least five hours a week in the past year. Future studies are needed to investigate how much experience with AVGs is needed to obtain enhancing effects, and to investigate for how long these effects last. Whereas playing videogames is a rather time-intensive manner to enhance cognitive performance, the next chapters study cognitive enhancement means that result in rather acute effects.

Food supplements

From the first three chapters, it may become clear that brain stimulation techniques in itself are promising tools if used correctly. However, further investigation is needed before they will ever be ready to be used commercially (if ever). In the next chapters, we therefore focus on an even safer and healthier method to enhance cognition: food supplements. Food supplements denote a nutrient or group of nutrients such as vitamins, minerals, proteins, fats or oils, that are meant to supplement, but not substitute, a healthy diet. They provide a safe, healthy, and easy way to modulate cognitive processes. This idea is not new though, as several decades ago the German philosopher Ludwig Feuerbach already claimed that “Der Mensch ist, was er iβt” (i.e., you are what you eat, 1862, as cited in Feuerbach, 1960). Feuerbach was probably the first to promote the idea that the food one eats affects a person’s state of mind. With the recent economical, societal and ideological developments of supporting health and remaining vital in aging, the idea that the food we eat influences the way we think and perceive the world has received increasing attention (e.g., think about all the “superfoods” that are on the market nowadays). In the remaining chapters, based on knowledge about the physical effects (i.e., metabolic, chemical, etc.) several food supplements are put forward as “cognitive enhancers”.

As discussed earlier, active tVNS enhanced action cascading performance, most likely through affecting GABA and NE neurotransmitter levels in the brain. However, the exact role of each separate neurotransmitter cannot be investigated using tVNS. That is, tVNS targets different neurotransmitters simultaneously, which makes it impossible to ascertain whether the observed effects resulting from tVNS are due to NE, GABA, or both. However, based on previous studies and theories as discussed in Chapter one, there is reason to believe that GABA plays a possible causal role in action cascading performance. In **Chapter five** therefore, it is investigated whether the intake of the food supplement GABA, which mimics the chemical structure of GABA and leads to increases of GABA in the brain, enhances action selection processes. That is, the general consensus is that action cascading processes rely on fronto-striatal networks, and GABA is likely to play an important role in the neuromodulation of action control processes. GABA plays a pivotal role in information encoding and behavioral control, in the regulation of motor functions, and in motor learning. More importantly, GABA also seems involved in action selection and response inhibition processes occurring in the frontal-striatal networks. Previous studies have also shown that superior performance in action cascading tasks is associated with increased concentrations of GABA in the brain. Taken together, these findings indicate an important role of GABA in the neuromodulation of action cascading processes, where slight increases of GABA are associated with better action cascading performance. In this chapter, it is indeed demonstrated that the intake of GABA directly influences the efficiency of action cascading. It is shown that the administration of a low dose of synthetic GABA reduced the time needed to change to an alternative response, regardless of whether this shift was required to occur simultaneously to a stopping process or when the stopping process had already finished. In addition, the intake of GABA reduced the time that people needed to inhibit the unwanted response. These findings offer substantial support for the idea of a crucial role of the GABA-ergic system in action cascading. Given that in daily life we are often confronted with multiple response options and need to efficiently prioritize and cascade our actions in order to successfully fulfill a task, this has important implications. That is, the intake of the food supplement GABA, and possibly foods containing GABA, could help to efficiently handle the ever-changing environment we are living in.

Building upon the previous chapter, action cascading involves a component called task-switching, in which dopamine (DA) seems to play an important role. **Chapter six** evaluates the intake of the amino acid tyrosine

(TYR), the chemical precursor of DA, as a method to enhance task-switching (i.e. cognitive flexibility). We suggest that TYR administration selectively counteracts DA depletion, a process in which performance levels decline corresponding to the decrease DA function in the brain: When exposed to a cognitively challenging task, the rate of DA synthesis rises and resources become depleted. Under these circumstances, TYR may provide the resources necessary to allow DA synthesis to carry on and DA to remain at a level that allows optimal performance. The findings from this study demonstrate that, when participants are given enough time to prepare to switch between the two tasks (i.e. proactive control), TYR improved performance and made participants significantly faster at switching, but not when the switching had to be done very rapidly (i.e. reactive control). Even though we need to be careful in interpreting a null effect, the absence of a reliable impact of TYR on the preparatory task-switching component might thus be taken to suggest that TYR has little effect on processes underlying the retrieval, implementation, and maintenance of task sets. As these functions are commonly attributed to the frontal dopaminergic pathway, we speculate that this pathway does not belong to the main targets of TYR-induced increases of DA. In contrast, the residual component of task-switching costs is likely to reflect the online resolution of conflict induced by inertia or stimulus-triggered reactivation of the old task set. The significant effect of TYR on the residual component can thus be taken to reflect TYR-induced support of processes underlying such conflict-resolving processes. Future studies are however needed to varify these interpretations.

In **Chapter seven,** the amino acid tryptophan (TRP), one of the most investigated amino acids and the chemical precursor of serotonin (5-HT), is introduced. TRP supplementation can increase 5-HT levels in the brain and for this reason, numerous studies have investigated whether administration of TRP can positively influence social behavior that relies on serotonergic function. It is thought that increasing levels of 5-HT leads to improvements in social functioning. In this chapter, it is demonstrated that the oral intake of TRP, supposedly increasing levels of 5-HT, increased the amount of money that subjects donated to charity. Importantly, charitable donating is defined as a prosocial behavior (i.e. behavior intended to help others such as such as helping, sharing, donating, and volunteering). Although preliminary, these findings may indicate that the intake of TRP promotes prosocial behavior, which could have important implications for society. That is, promoting prosocial behavior by stimulating the intake of TRP may benefit society as a whole.

Based on the previous chapter, **Chapter eight** provides a review of TRP as a modulator of social behavior. In this chapter, the available studies on TRP supplementation are reviewed to clarify if, and under what circumstances, TRP supplementation might modulate social behavior. A rising theory in this field is that TRP re-biases attention away from negative stimuli and towards more positive ones, which fits also with the findings that TRP and 5-HT play important roles in affective processing. Consistent with that, studies demonstrate that TRP supplementation seems to improve control over social behavior in patients and individuals suffering from disorders or behaviors associated with dysfunctions in serotonergic functioning. In contrast, in healthy humans TRP supplementation seems to promote social behavior. Although more research is needed to disentangle and understand the relations between individual differences (e.g. metabolic rate and pathways, genetic predisposition, enzymatic activity, gender, age, etc.), 5-HT functioning, and social interactions, TRP seems a promising tool for modulating social behavior. Even though the food supplements (i.e., GABA, TYR, TRP) put forward in these chapters were administered in pure form, these amino acids are also naturally present in our food. Although more research is needed to understand how these amino acids affect cognition and behavior when administered through food (which always contains other ingredients as well), together, these chapters seem to support the idea that the food we eat may have important implications for our cognition and behavior.

The idea that the food we eat affects the way we think and perceive the world, which can then be used to enhance cognitive and social functioning, is further supported by the existence of the ‘gut-brain axis’, which involves bidirectional communication via neural, endocrine and immune pathways between the brain and the intestines. In recent years it has become increasingly evident that this communication also involves interactions with the intestinal microbiota, which release immuneactivating and other signaling molecules that may play an important role in regulating the brain and behavior. These novel insights have fueled the hypothesis that modification of microbial ecology, for example by supplements containing microbial species (probiotics), may be used therapeutically to modify stress responses and symptoms of anxiety and depression. The increasing incidence of depression is alarming and development of preventive measures has been identified as a priority (World Health Organization, 2012). According to cognitive theories of depression, cognitive reactivity plays a central role in the development, maintenance, and recurrence of depression and therefore is a relevant target for interventions. **Chapter nine** therefore focuses on the question whether probiotics can reduce cognitive reactivity to sad mood (i.e. vulnerability to develop a depression) in healthy participants not currently diagnosed with a mood disorder. Results of this chapter demonstrate that, compared to participants who received a placebo intervention, participants who received a 4-week multispecies probiotics intervention showed a significantly reduced overall cognitive reactivity to sad mood, which was largely accounted for by reduced rumination and aggressive thoughts. These results provide the first evidence that the intake of probiotics may help reduce negative thoughts associated with sad mood. As cognitive reactivity seems to be critical in determining whether sad mood will be a transient state or will become protracted, thus increasing the risk of developing clinical depression, probiotics supplementation warrants further research as a potential preventive strategy for depression.

To conclude this overview, the chapters presented in this dissertation provide further evidence for the idea that brain stimulation, video gaming, and food supplements provide promising tools in enhancing cognitive performance and social behavior in healthy humans. In addition, important insights in the (possibly) underlying mechanisms of the effects of enhancement techniques, which are needed if we ever want to be able to apply these methods in other fields, are provided.

Openness in science

This dissertation supports the mission of the Center for Open Science (COS) to increase openness, integrity, and reproducibility of scientific research. The (raw) data of all studies reported in this dissertation are therefore stored in the Open Science Framework (OSF). This data can be accessed with the following web links:

Chapter 1 : Transcutaneous vagus nerve stimulation (tVNS) enhances response selection during action cascading processes.
https://osf.io/xed5m/?view_only=84789d588e48409cb4d61e638ba6489f

Chapter 2 : Transcutaneous vagus nerve stimulation (tVNS) does not increase prosocial behavior in Cyberball.
https://osf.io/wb2zt/?view_only=032e4ab33218414085c5e90b443e5877

Chapter 3 : "Unfocus" on foc.us: Commercial tDCS headset impairs working memory.
https://osf.io/43kix/?view_only=423f8fe402af43aa86e2155d47d50a8e

Chapter 4 : Action video gaming and cognitive control: playing first person shooter games is associated with improved action cascading but not inhibition.
https://osf.io/sbvni/?view_only=8bec928941724b30acbfa1d9302be434

Chapter 5 : γ-Aminobutyric acid (GABA) administration improves action selection processes: a randomized controlled trial.
https://osf.io/8g3hr/?view_only=7b4ceb65be744cc286c5d07c6d9d48d3

Chapter 6 : Tyrosine promotes cognitive flexibility: Evidence from proactive vs. reactive control during task switching performance.
https://osf.io/aqrzb/?view_only=906a14b7676145278728a6a2cbfb24ef

Chapter 7 : Tryptophan promotes charitable donating.
https://osf.io/6szjq/?view_only=b31635d6bed544a29d545a21f5832479

Chapter 8 : Tryptophan supplementation modulates social behavior: a review.
Not applicable

Chapter 9 : A randomized controlled trial to test the effect of multispecies probiotics on cognitive reactivity to sad mood.
https://osf.io/enxmq/?view_only=ff13ba53293246bc82d09568515ca193