Lorenza S. Colzato

Theory-Driven Approaches to Cognitive Enhancement

Springer

Theory-Driven Approaches to Cognitive Enhancement

Lorenza S. Colzato

Theory-Driven Approaches to Cognitive Enhancement

Springer

Lorenza S. Colzato
Cognitive Psychology Unit and Leiden
Institute for Brain and Cognition
Leiden University
Leiden
The Netherlands

ISBN 978-3-319-57504-9 ISBN 978-3-319-57505-6 (eBook)
DOI 10.1007/978-3-319-57505-6

Library of Congress Control Number: 2017938558

Printed on acid-free paper

This Springer imprint is published by Springer Nature
The registered company is Springer International Publishing AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

To my husband Bernhard,
my soulmate, the love of my life,
you believed in me before anyone else did
or when no one else would

Preface

"The mind is the limit. As long as the mind can envision the fact that you can do something, you can do it, as long as you really believe 100%"—this is a quote that I like to repeat myself before every challenging (physical or mental) situations in order to get the best performance out of me. In research, teaching or sport, my ultimate goal is not to outperform others but to always get better for my own sake. This is for me the essence of cognitive enhancement: the use of any (legitimate) means (e.g., video game, brain stimulation, neurofeedback, physical exercise or food supplements) to reach one's personal best.

Why having a book about cognitive enhancement now? Why has this topic become so relevant in the past few years?

Economically, the interest in cognitive enhancement is mainly driven by the increasing costs of the welfare system, especially with regard to the increasing age of citizens in Western societies. For instance, cognitive enhancement can help to delay cognitive decline in the elderly, which would extend the time people can live autonomously and, thus, reduce the welfare costs for the time thereafter. Along the same lines, training children could speed up the education of healthy individuals and reduce the risk of behavioral deviance and pathology, again with considerable savings for welfare and education systems. But there is also a more ideological reason for the increased interest in cognitive enhancement. Both Eastern and Western societies are continuously driven towards more individualism, which emphasizes the existence and often also the importance of individual differences over commonalities and collectivistic values. These tendencies go hand-in-hand with ideological developments in public opinion and within political parties, which in many countries have gravitated towards more neoliberal, individualism-heavy positions over the last 15 years or so. Among other things, this has involved a rather systematic deconstruction of the welfare system and established the view of the individual as an architect of his or her own life. Research on cognitive enhancement has benefited from both aspects of this trend. The economic problems of the welfare system have boosted the interest in procedures and activities that make welfare societally more affordable, and the ideological turn towards individualism provides a natural breeding ground for the public interest in procedures and activities that help to express and to further develop individual needs and interests.

The widespread use of smart phones has led to a real explosion of "apps" to enhance cognitive functioning, ranging from simple alerts reminding the elderly to take her/his pill to theoretically guided programs to systematically enhance specific cognitive functions. Industry and funding agencies have taken notice of the many opportunities these techniques can open, and the current European Research Area (ERA in Horizon 2020) has various calls to promote gamification. Along the same line, President Obama declared already in 2011 the importance of investing money in educational technology and realized the enhancing potential of gaming. Indeed, as quoted from the White House initiative "Games that Can Change the World": "Games for impact are designed to be at once entertaining and engaging, and also something more: educational, enlightening, and perhaps even designed to motivate action." Clearly, this is likely to strengthen this trend further in the near future, but I think that the full potential of gamification is not always sufficiently appreciated. Turning psychological experiments and training procedures into apps is certainly handy for both researchers and users, especially as it allows integrating cognitive enhancing programs better with real-life circumstances. Another example to demonstrate how ERA is focusing on cognitive enhancement is the Joint Programming Initiative "A healthy diet for a healthy life" which is funding research on how nutrients can prevent (social) cognitive decline in normal aging. This initiative is particularly emblematic in showing how economic problems of the welfare system have boosted the interest in procedures and activities that make welfare societally more affordable.

Need for Theory

Kurt Lewin's claim that "nothing is as practical as a good theory" is the *leitmotif* of this book about cognitive enhancement. While in the past the field of cognitive enhancement used mainly effect-driven approaches (that seek to demonstrate that an enhancing intervention can have an effect without explaining how it modulates the targeted function and why some people benefit more than others), this book proposes a mechanistically oriented, theory-driven approach that tries to understand and explain individual differences to a degree that allows a comprehensive understanding of how a particular intervention modulates cognition.

Structure of the Book

The present book aims to present different means to enhance cognition and to get a better understanding of the underlying mechanism of *how* those means modulate our behavior. According to the similarities of the mechanism of action, the book is divided into six parts.

The first and second part are devoted to food supplements and/or drugs that acting on increasing the level of a particular neurotransmitters are able to enhance those cognitive functions modulated by them. The focus of the third part is on noninvasive brain stimulation methods which are used to stimulate regions of the brain related to cognitive functions targeted by the enhancing intervention. The fourth part is dedicated to neuronal entrainment methods by means of which, in order to optimize performance, the brain "takes over" or synchronizes its activity based on external or internal stimulation. The fifth part addresses far transfer interventions which underlying idea suggests that individuals are getting better not only in skills related to their practice of preference, but also in entirely unrelated skills. The fifth part aims to explore environmental factors which, under particular circumstances, are known to promote cognitive performance. The sixth part is about environmental factors able to promote cognitive performance. The seventh part considers "real-life" examples in which the concept of cognitive enhancement has been successfully applied. Finally, the last part is dedicated to the costs and benefits associated with cognitive enhancement.

Leiden, The Netherlands Lorenza S. Colzato

Acknowledgements

To me cognitive enhancement is more than science, it is a *lifestyle*. Many people have helped me and enhanced me on the road to this book and I must express my deepest gratitude to a few of them:

My editor Lilith Dorko for giving me this opportunity.
The external contributors and co-authors of this book for their professionalism and enthusiasm.
Vera Mekern and Olga Boer for having made such fantastic illustrations and figures.
Roberta Sellaro, Bryant Jongkees and Laura Steenbergen for being a "dream" team to work with.
Gabriella Vigliocco, Susanne Jaeggi and Teresa Bajo for being a role model for women in science. I look up to you.
Onur Güntürkün and Oliver Wolf for supporting women in science. I owe you.
Christian Beste, Armin Kibele, Sander Nieuwenhuis and Hester Bergsma for always being there for me when it counted.
Asher Cohen for having taught me to stand up for what is right.
Claudia Pama, Claudia Rossi Paccani and my ex-students for having made a better teacher and person out of me.
The Netherlands Organization for Scientific Research (NWO) for supporting my research.

On a personal note, these people deserve a special mention:

Meine Nichten Lilu, Amelie, Cosma und mein Neffe Linus. Ich hab euch lieb.
Alessandra, Cristina, Fortunata, Stefania, Daniela, Sabrina e le amiche di una vita perché questi pezzi di passato che ritornano sono parti di quello che eravamo e che ancora siamo…

Contents

Author and Contributors

About the Author

Lorenza S. Colzato Ph.D. is Professor by Special Appointment of Cognitive Enhancement at Ruhr University Bochum (Germany). She is also Senior Research Fellow at the Institute for Sports and Sport Science at University of Kassel (Germany) and at the Institute of Psychological Research at Leiden University (The Netherlands). Dr. Colzato is a recipient of two Innovational Research Incentives Scheme grants (VENI; VIDI) from the Netherlands Organization for Scientific Research. These grants are awarded only to "outstanding individuals of exceptional talent and originality who have a great enthusiasm for the conduct of challenging, groundbreaking research." Dr. Colzato is the founding Editor and current Editor-in-Chief of *Journal of Cognitive Enhancement*, which publishes articles on enhancement of human perception, attention, memory, cognitive control and action. She published over 150 articles in international peer-reviewed journals. Her research has been featured in TIME and in the Huffington Post US.

Dr. Colzato's current research activities focus on interventions (e.g., brain stimulation, meditation, physical exercise, life style, or food supplements) aimed at enhancing performance in healthy individuals.

Contributors

Ronald Andringa Department of Psychology, Florida State University, Tallahassee, FL, USA

Fréderique E. Arntz Cognitive Psychology Unit and Leiden Institute for Brain and Cognition, Leiden University, Leiden, The Netherlands

Guido P.H. Band Cognitive Psychology Unit and Leiden Institute for Brain and Cognition, Leiden University, Leiden, The Netherlands

Olga D. Boer Cognitive Psychology Unit and Leiden Institute for Brain and Cognition, Leiden University, Leiden, The Netherlands

Walter R. Boot Department of Psychology, Florida State University, Tallahassee, FL, USA

Joyce J. de Bruin Health, Medical and Neuropsychology Unit and Leiden Institute for Brain and Cognition, Leiden University, Leiden, The Netherlands

Rouwen Cañal-Bruland Institute of Sport Science, Friedrich-Schiller-University Jena, Jena, Germany

Leila Chaieb Department of Epileptology, University of Bonn, Bonn, Germany

Stefanie Enriquez-Geppert Department of Clinical and Developmental Neuropsychology, Faculty of Behavioural and Social Sciences, University of Groningen, Groningen, The Netherlands

Juergen Fell Department of Epileptology, University of Bonn, Bonn, Germany

Bernhard Hommel Cognitive Psychology Unit and Leiden Institute for Brain and Cognition, Leiden University, Leiden, The Netherlands

René J. Huster Department of Psychology, University of Oslo, Oslo, Norway

Armin Kibele Institute for Sports and Sport Science, University of Kassel, Kassel, Germany

Peter Kirsch Department of Clinical Psychology, Central Institute of Mental Health, Mannheim, Germany

Janna Katharina Kullmann Institute of Experimental Psychology, Heinrich-Heine University, Düsseldorf, Germany

Jonna Loeffler Department Performance Psychology, Institute of Psychology, German Sport University Cologne, Cologne, Germany

Vera Mekern Cognitive Psychology Unit and Leiden Institute for Brain and Cognition, Leiden University, Leiden, The Netherlands

Ana Beatriz Rodríguez Moratinos Departamento de Fisiología, Facultad de Ciencias, Universidad de Extremadura, Badajoz, Spain

Rebecca Mourits Cognitive Psychology Unit and Leiden Institute for Brain and Cognition, Leiden University, Leiden, The Netherlands

Michael A. Nitsche Department of Clinical Neurophysiology, Georg-August University Göttingen, Göttingen, Germany; Leibniz Research Centre for Working Environment and Human Resources, Dortmund, Germany; Department of Neurology, University Medical Hospital Bergmannsheil, Bochum, Germany

Kerwin J.F. Olfers Cognitive Psychology Unit and Leiden Institute for Brain and Cognition, Leiden University, Leiden, The Netherlands

Martin Reuter Department of Differential and Biological Psychology, Center for Economics and Neuroscience, University of Bonn, Bonn, Germany

Tomas Ros Laboratory for Neurology and Imaging of Cognition, Department of Neurosciences, University of Geneva, Geneva, Switzerland

Rebecca S. Schaefer Health, Medical and Neuropsychology Unit and Leiden Institute for Brain and Cognition, Leiden University, Leiden, The Netherlands

Katrin Schlauch Institute of Experimental Psychology, Heinrich-Heine University, Düsseldorf, Germany

Roberta Sellaro Cognitive Psychology Unit and Leiden Institute for Brain and Cognition, Leiden University, Leiden, The Netherlands

Iris Spruit Cognitive Psychology Unit and Leiden Institute for Brain and Cognition, Leiden University, Leiden, The Netherlands

Carlotta Stern Department of Psychology, University of Kassel, Kassel, Germany

Christina Trepkowski Institute for Experimental Psychology, Heinrich-Heine University Düsseldorf, Düsseldorf, Germany

Antonino Vallesi Department of Neuroscience, University of Padova, Padua, Italy; San Camillo Hospital IRCCS, Venice, Italy

Kristl Vonck Laboratory for Clinical and Experimental Neurophysiology, Neurobiology and Neuropsychology, Department of Neurology, Ghent University Hospital, Ghent, Belgium

Pauline van der Wel Cognitive Psychology Unit and Leiden Institute for Brain and Cognition, Leiden University, Leiden, The Netherlands

Tamara Wild Institute of Experimental Psychology, Heinrich-Heine University, Düsseldorf, Germany

Guilherme Wood Department of Neuropsychology, University of Graz, Graz, Austria


CHOLINE
500MG
TRYPTOPHAN
Choline
tyrosine
CHOLINE
500MG
food supplements
TYROSINE
TRYPTOPHAN
tyrosine
CHOLINE
500MG
Choline
are we what we eat?
tyrosine
CHOLINE
500MG
TRYPTOPHAN
TYROSINE
TRYPTOPHAN
TRYPTOPHAN
Choline
CHOLINE
500MG
tyrosine
CHOLINE
500MG

Part I
Food Supplements—Are We What We Eat?

Introduction

The present part aims to explore the strategy to enhance cognitive processes by means of a particular diet and/or the intake of freely available food supplements. In a seminal essay, the German philosopher Ludwig Feuerbach (1862) claimed that "Der Mensch ist, was er iβt" (you are what you eat). Feuerbach was probably the first intellectual to promote the idea that the food one eats has a bearing on one's state of mind. This idea later became the motto of the hippie culture, which promoted eating organic and healthy food. Since then, the idea that the food we consume modulates the way we think and perceive the world has been very suggestive in popular culture and the focus of scientific research.

According to recent Euromonitor International market analysis (2016), over the last decade, sales of food supplements have raised. Globally, the market is now valued at $82 billion, with roughly 28% of that in the U.S., where sales expanded by approximately $6 billion between 2007 and 2012. Growth is expected to remain strong through 2017—between 5 and 6% a year, both globally and in the U.S.

Responsible for this phenomenon are different factors. First of all, because of the increasing costs of the welfare system people are more aware and receptive for preventative healthcare. In particular, the rise of food supplement sales seems to be associated with the increment of online health information which is taken by users like serious and validated medical advice. Indeed, the ideological turn towards more individualism of both the Eastern and Western societies has benefited this flourishing market because many supplement purchases are the result of users taking their health into their own hands, not the direct advice of a doctor. Not surprisingly, in order to counteract cognitive and physical decline, a growing consumer population is the elderly. As reported by Euromonitor International, consumers of 65 and older accounts for more than one-third of global food supplement sales, a trend that is expected to continue for the foreseeable future. Lastly, the increase of restricted diets, such as the vegan diet, has boosted the consumptions of food supplements and

fortified and enriched food to compensate for the lack of essential nutrients like vitamin B12 and the amino acid choline.

This part is devoted to three of the most investigated food supplements known to benefit performance. First, by means of its effect on the dopaminergic system, the enhancing effect of the amino acid tyrosine on executive functions is elaborated in Chapter "Tyrosine". Second, through its effect on the serotonergic system, the evidence of the beneficial intake of the amino acid tryptophan on social cognition is discussed in Chapter "Tryptophan". Lastly, in Chapter "Choline", how the amino acid choline, chemical forerunner of the neurotransmitter acetylcholine, may facilitate memory processes will be illustrated.

References

Euromonitor International. (2016). *Market analysis vitamins and dietary supplements*. Retrieved from: http://www.euromonitor.com/vitamins-and-dietary-supplements

Feuerbach, L. A., [1862]. (1960). Das Geheimnis des Opfers oder der Mensch ist was er ißt. In W. Bolin & F. Jodl (Eds.), *Ludwig Feuerbach Sämtliche Werke* (Bd.X, pp. 41–67). Stuttgart-Bad Canstatt: Frommann Verlag.

RETRACTED CHAPTER: Tyrosine

Lorenza S. Colzato

Introduction

The amino acid L-tyrosine (TYR) is the chemical forerunner of dopamine (DA). Under specific circumstances, TYR administration can augment DA levels in the brain (Cuche et al. 1985; Gibson and Wurtman 1977; Tam et al. 1990) and because of that several studies have investigated whether the supplementation of TYR can have a beneficial effect on cognitive and behavioral performance that depends on DA function. However, outcomes on the effectiveness of TYR supplementation are mixed: some studies show positive effects, whereas others do not. The present chapter, adapted from Jongkees et al. (2015), reviews the available TYR studies to elucidate under which conditions TYR has a beneficial effect on cognitive performance. The focus will be on healthy humans and not on clinical populations associated with suboptimal catecholamine levels.

First, I will describe how TYR supplementation impacts DA function, given that the nature of this mechanism may play a pivotal role in determining whether and to what extent supplementation can promote performance. Second, I will outline the available studies on stress, which decreases DA levels in the brain via increased turnover rates and leads to associated impairments in performance (Lehnert et al. 1984; Mahoney et al. 2007). Accordingly, TYR administration has been suggested as a potential counter-actor of stress-induced decline in performance. Third, I will review studies on healthy humans in cognitively demanding situations, which

The original version of this chapter was retracted: The retraction note to this chapter is available at https://doi.org/10.1007/978-3-319-57505-6_24

L.S. Colzato (✉)
Cognitive Psychology Unit and Leiden Institute for Brain and Cognition, Leiden University, Leiden, The Netherlands
e-mail: colzato@fsw.leidenuniv.nl

L.S. Colzato
Institute of Cognitive Neuroscience, Faculty of Psychology, Ruhr University Bochum, Bochum, Germany

L.S. Colzato, *Theory-Driven Approaches to Cognitive Enhancement*,
https://doi.org/10.1007/978-3-319-57505-6_1

create a stress-like state that might lead to DA depletion and associated cognitive decline that might be reversed by TYR administration. The outcomes of the reviewed studies point out that TYR supplementation has the potential to promote cognitive performance, particularly in short-term stressful and/or cognitively demanding situations and when individual differences related to DA baseline levels are taken into account.

Mechanism of Action

Plasma TYR levels peak between 1 and 2 h after ingestion and can stay significantly elevated up to 8 h (Glaeser et al. 1979). Accordingly, in rats it has been found that prefrontal DA was raised 1 h after TYR intake, but not earlier (Tam et al. 1990). Once it has passed the blood–brain barrier and is taken up by the appropriate brain cells, the enzyme tyrosine-hydroxylase (Daubner et al. 2011) converts TYR into L-DOPA. At first tyrosine-hydroxylase activity increases upon consumption of TYR, but its activity is downregulated by end-product inhibition (Daubner et al. 2011; Tam et al. 1990), which prevents large increases in DA release. In a second step, L-DOPA is converted into DA leading to an elevation in DA level, see Fig. 1.

Notably, TYR has been shown to enhance neurotransmitter synthesis only in actively firing neurons (Fernstrom and Fernstrom 2007; Lehnert et al. 1984; Tam et al. 1990). This points to the fact that TYR can counteract neurotransmitter depletion, a process in which enhanced brain activity induces decrements in DA levels and associated behavioral performance decline. Indeed, when subjected to stress or a cognitively challenging task, DA neurons become more active and their synthesis rate raises (Kvetnansky et al. 2009; Lehnert et al. 1984; Mahoney et al. 2007). As a result, more DA is synthesized from TYR in order to meet the situational demands. However, the conversion of TYR into DA becomes limited when TYR levels decline. This process is responsible for less DA availability and resulting declines in performance (Goldman-Rakic et al. 2000; Muly et al. 1998). In this situation, brain function might benefit from TYR administration, which allows DA synthesis to carry on and maintain DA levels necessary to guarantee optimal performance (Wurtman et al. 1981). This role of TYR as a *depletion counter-actor* seems to take place only in actively firing neurons. Indeed, in rats it has been demonstrated that TYR supplementation only increased DA synthesis in the striatum when this region was pharmacologically activated (Tam et al. 1990). That is, TYR administration seems to have a positive effect only in circumstances that encourage neurotransmitter synthesis, i.e., circumstances that are sufficiently stressful or challenging. Accordingly, this chapter will show that TYR's role as a *depletion counter-actor* corresponds to the outcomes found in the literature.

The World Health Organization's daily upper requirement of TYR is 14 mg/kg (see Deijen 2005), suggesting that an individual weighing 70 kg should consume daily about 1 g of TYR for normal functioning. It is questionable whether doses above 1 g are likely to add any further benefits, given that the rate-limiting tyrosine-hydroxylase enzyme is supposed to be close to saturation in normal

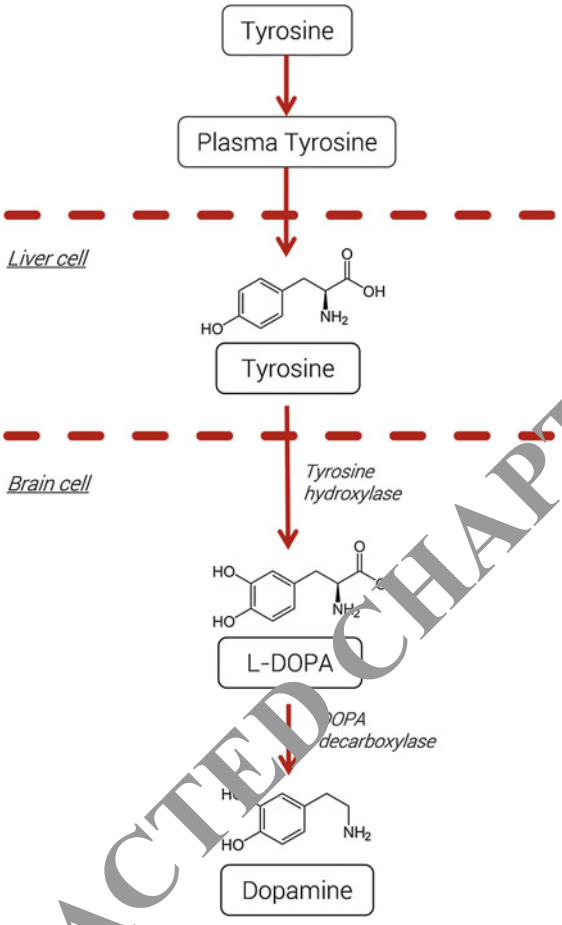


Fig. 1 Schematic representation of the effect of acute tyrosine supplementation on tyrosine to dopamine conversion. Once it has passed the blood–brain barrier the enzyme tyrosine-hydroxylase converts tyrosine into L-DOPA. In a second step, L-DOPA is converted, via the enzyme DOPA decarboxylase, into dopamine leading to an elevation in dopamine level

competition (Brodnik et al. 2012). Indeed, TYR transport across cell membranes is reduced in healthy humans after TYR administration (Wiesel et al. 1999). That is, extra TYR would thus be metabolized rather than converted into L-DOPA. While too much TYR might not contribute to additional benefits, consuming too little might also not be beneficial. Moreover, TYR shares a transporter across the blood–brain barrier with several other large neutral amino acids such as phenylalanine and tryptophan (Fernstrom 1990). Accordingly, the amount of TYR that crosses the blood–brain barrier instead of being metabolized peripherally relies on the individual's levels of these other amino acids. Studies exploring the effect of acute TYR administration should thus have their subjects fast overnight to limit competition

from other amino acids. However, in long-term studies this is not advisable given that completely avoiding these other amino acids for longer periods might not be feasible nor recommendable.

One may argue that L-DOPA might be preferable to TYR because it circumvents issues such as the competition from other amino acids and the rate-limiting tyrosine-hydroxylase. Nonetheless, there are a number of factors why TYR supplementation might be more suitable. On the one hand, the fact that the tyrosine-hydroxylase enzyme is already close to saturation under normal circumstances has the advantage to prevent large quantities of TYR be converted. In contrast, the conversion of L-DOPA into DA does not rely on a similar rate-limiting factor, which significantly increases the possibility of leading to "overdose" DA levels that are harmful for performance (Goldman-Rakic et al. 2000; Muly et al. 1998). Taking into account the inverted-U profile of DA (Cools and D'Esposito 2011), it is likely for L-DOPA supplementation to boost individuals to the lower right end of the curve, while the subtle increment from TYR is unlikely to lead to any "overdose" effect. There are currently no established side-effects of long-term TYR administration, even though one study found more saccadic intrusions during smooth-pursuit eye movement performance in patients with schizophrenia (Deutsch et al. 1994). On the other hand, chronic L-DOPA supplementation has been linked to adverse side-effects such as insomnia, dyskinesia, nausea, and in some cases even psychosis (Foster and Hoffer 2004; Leggins et al. 2012). It should be acknowledged that studies on the chronic effect of TYR administration are still limited and its potential long-term side-effects should be more extensively explored before inferring final conclusions. Notably, even though the beneficial effects of TYR during long-term stress are less investigated, the outcomes are encouraging. It has been shown that prolonged stress exposure (e.g., low temperatures) can enhance TH activity up to one month, suggesting TYR might be especially useful during winter. After one month, however, tyrosine-hydroxylase activity is no longer significantly elevated (Kvetnansky et al. 2009). Nonetheless, DA neurons stay highly active, leading to a depletion of DA levels (Kvetnansky et al. 2009). This result indicates that TYR can also have positive effects in long-term situations. Along the same line, a study in Antarctica residents (Palinkas et al. 2007) found TYR to exhibit beneficial effects even after 7 weeks of exposure to extreme cold.

Enhancing Cognitive Performance in Stressful Conditions

Stress causes enhanced DA activity and turnover rates in the brain, inducing the depletion of DA levels as well as behavioral depression (Kvetnansky et al. 2009; Lehnert et al. 1984). Nonetheless, studies that supplemented TYR to rats before stress exposure have shown that DA depletion and declines in performance can be compensated (Lehnert et al. 1984; Lieberman et al. 2005; Rauch and Lieberman 1990; Shurtleff et al. 1993; Yeghiayan et al. 2001). These outcomes inspired several studies exploring whether and under which circumstances TYR can also promote

human performance during stress. These studies often targeted either physical exercise or cognitive functions.

Studies on TYR and physical exercise have primarily targeted endurance exercise, postulating that sustaining adequate DA levels in the brain can maintain the incentive to optimize performance. Two studies have explored TYR and endurance exercise without an additional overt stressor, but neither found any enhancement after TYR supplementation (Chinevere et al. 2002; Sutton et al. 2005). Other studies have examined exercise performance during heat exposure, but the outcomes were inconsistent. One study showed TYR induces longer exercise times in the absence of an increase in ratings of perceived effort and thermal sensation (Tumilty et al. 2011), indicating that TYR did indeed enhance endurance. Nonetheless, these outcomes were not replicated in two later studies (Tumilty et al. 2014; Watson et al. 2012). Hence, there is no reliable evidence TYR promotes physical exercise performance, e.g., endurance, in stressful circumstances. This suggests that physical performance *can* be promoted by TYR administration, but only under specific circumstances that activate DA neurons and mobilize higher cognitive functions such as attention and cognitive control. That is, TYR administration seems to enhance physical performance only when it recruits individual high enough cognitive demands that lead to DA depletion. Accordingly, studies exhibiting no effect of TYR might then have investigated exercise that did not sufficiently recruit cognitive processes. This hypothesis is supported by several outcomes showing that TYR is effective at promoting cognition during stress, as discussed below.

It is noteworthy, in contrast to the above-mentioned studies, TYR reliably has a beneficial effect on cognitive performance when healthy humans ingest TYR before stress exposure. In such studies, hypothermia is often used as a stressor and TYR has been consistently shown to counteract the decrements in cognition it may cause (Mahoney et al. 2007; O'Brien et al. 2007; Shurtleff et al. 1994). These studies explored working memory, a key cognitive function that entails actively maintaining and updating information in memory (Baddeley and Hitch 1974; Miyake et al. 2000). Given that working memory is modulated by DA (Cools et al. 2008; Goldman-Rakic et al. 2000; Moustafa et al. 2008; Siessmeier et al. 2006), this function has been often investigated in relation to TYR. In particular, changes in DA levels due to TYR are expected to modulate working memory performance. All studies described cold exposure to reduce working memory performance; however, this decline was counteracted when the participants were administered TYR. Banderet and Lieberman (1989) investigated TYR and exposure to cold in relation to a broad range of cognitive functions. The authors described benefits in vigilance and reaction times on several tasks. Interestingly, they restricted their analysis to "those individuals most affected by exposure to the cold" (p. 760), indicating TYR only enhances individuals who would otherwise have been stressed by the coldness. This possibility highlights the utility of taking into account individual differences when examining the effects of TYR (Jongkees et al. 2014). Along the same lines, performance on the Stroop task and working memory has been promoted by TYR administration while participants were exposed to an auditory stressor (Deijen and Orbleke 1994). Similarly, performance on working memory, reasoning, and vigilance has been enhanced by TYR during sleep deprivation (Magill et al. 2003).

Moreover, TYR has also been found to enhance both cognitive and behavioral performance in army cadets after an intensive combat training course. Nonetheless, it is hard to draw conclusions from this study, given that many other amino acids were administered jointly with TYR and the placebo-group did not receive a completely neutral placebo (Deijen et al. 1999).

Finally, some studies have explored whether TYR can counteract stress-induced mood declines. Palinkas et al. (2007) administered TYR to residents of Antarctica, with the goal to enhance mood during protracted cold climate exposure. The hostile environment of Antarctica can be regarded a multi-stressor intervention including confinement and isolation as well as the inherent cold. Notably, Palinkas and colleagues showed that TYR improved mood, but only during the winter. This study is one of few that investigates TYR administration in healthy individuals in a long-term situation. The outcome is in line with the result by Banderet and Lieberman (1989) that TYR counteracted cold-induced decrements in mood. On the contrary, TYR did not to enhance mood without stress exposure (Leathwood and Pollet 1983; Lieberman et al. 1983). These outcomes indicate TYR might have a positive effect on mood, but only in stressful situations such as extreme cold.

In sum, the beneficial effects of TYR on cognitive performance are likely due to TYR counteracting a decline of DA availability during stress (Banderet and Lieberman 1989; Kvetnansky et al. 2009; Lehnert et al. 1984), which precludes declines in higher cognitive functions such as attention and working memory. For instance, TYR's enhancing effect on working memory and attention, found in many studies, might be due to TYR supporting an optimal level of DA necessary for a balance between stable cognitive representations versus flexible updating of those representations (Cools and D'Esposito 2011).

Enhancing Cognitive Demands in Healthy Humans

This section reviews studies on TYR administration in healthy humans who were not explicitly and directly exposed to stressors that may affect their performance. Rather, these studies included challenging cognitive tasks that were assumed to be demanding enough to lead to a stress-like state that causes DA depletion and decreased levels of performance, an effect TYR may reverse.

In line with the above-mentioned studies on stress, so far, two studies have found that TYR can promote working memory performance, but in the absence of a direct exposure to stress. Rather, beneficial effects were only found under particularly demanding circumstances. In particular, Thomas et al. (1999) found TYR only enhanced working memory when other tasks were performed at the same time. Moreover, TYR has been found to enhance working memory even in a single-task setting, but only in the task's more challenging condition that places a higher load on memory (Colzato et al. 2013). The outcomes of these two studies support the idea that TYR can enhance cognitive performance and emphasize the crucial role of TYR as counter-actor in performance-degrading conditions.

In addition to working memory, Colzato et al. (2014) have found TYR to selectively enhance the ability to stop on time (an index of inhibitory control) without affecting response execution. Moreover, a new study has found that TYR can enhance cognitive flexibility as indexed by a task-switching paradigm: TYR likely promoted performance by supporting conflict-resolving processes that may have in other circumstances produced a stressful state (Steenbergen et al. 2015). Furthermore, TYR has also been found to enhance performance on a convergent-thinking task (Colzato et al. 2015). All three above-mentioned studies are particularly relevant because the cognitive functions investigated are assumed to depend on DA-driven cognitive control (Cools and D'Esposito 2011). Hence, these outcomes point to the possibility that positive effects induced by TYR may be mediated by increased DA function. None of the studies describes an effect of TYR on mood, but this was expected given that mood was not reduced even in the placebo conditions, so there was no decline to reverse.

Finally, a recent study for the first time took into account individual differences (i.e., genetic differences) in base levels of DA to explain the effectivity of TYR. Indeed, it is likely that depending on this DA baseline levels, some people may benefit more than others from TYR intake (Jongkees et al. 2014). The study showed evidence supporting the idea that TYR supplementation may function as a cognitive enhancer and compensate for unfavorable genetic predisposition. TYR was administered to participants, genotyped for the C957T polymorphism at the DRD2 gene (polymorphism related to the striatal DA level). Measures of working memory updating and inhibitory control were acquired. T/T homozygotes (i.e., individuals associated with lower striatal DA level) showed larger beneficial effects of TYR supplementation than C/C homozygotes (i.e., individuals associated with higher striatal DA level). These findings reinforce the idea that genetic predisposition modulates the effect of TYR in its role as cognitive enhancer (Jongkees et al. 2014; Colzato et al. 2016).

In sum, the outcomes described in this section suggest TYR can improve cognitive performance without direct exposure to stress, but only if performance would normally be impaired by high cognitive demands. Indeed, high cognitive challenges lead to a stress-like state inducing DA depletion and associated cognitive impairments, which are then reversed by TYR. Moreover, the effectivity of TYR seems to depend on individual DA baseline levels.

Conclusion

TYR, the chemical forerunner of DA, has the promising potential to increase DA function in the brain in challenging situations. The mechanisms of action of TYR are to help the brain to maintain an elevated rate of DA synthesis when the brain needs it the most.

The potential of TYR for enhancing physical exercise during stress seems restricted; probably because physical performance is not as straight related to DA levels in the brain as cognitive performance is. Accordingly, this suggests physical

exercise may profit from TYR only to the degree that it recruits a stressful state in which cognitive control functions are required and DA levels are reduced.

TYR seems to show the most reliable beneficial effects on cognitive performance when healthy humans are exposed to either external stressors or cognitively challenging circumstances. Under these conditions, DA levels in the brain decrease and, consequently, performance on cognitive tasks declines. TYR supplementation acts as a cognitive enhancer by refilling DA levels in the brain and compensate for the stress-induced impairment of a variety of cognitive functions. This improvement is modulated by DA baseline levels (i.e., genetic differences) and is due to an increase of DA function in striatal or prefrontal areas, which is closely associated with cognitive control functions, such as cognitive flexibility, working memory updating, and response inhibition.

In nutshell, TYR seems to be a very promising cognitive enhancer but only when individuals find themselves in stressful or cognitively demanding situations and, in particular, when individual differences are taken into account.

References

Baddeley, A. D., & Hitch, G. (1974). Working memory. In G. H. Bower (Ed.), *The psychology of learning and motivation: Advances in research and theory* (pp. 47–89). New York: Academic Press.

Banderet, L. E., & Lieberman, H. R. (1989). Treatment with tyrosine, a neurotransmitter precursor, reduces environmental-stress in humans. *Brain Research Bullettin, 22,* 759–762.

Brodnik, Z., Bongiovanni, R., Double, M., & Jaskiw, G. E. (2012). Increased tyrosine availability increases brain regional DOPA levels in vivo. *Neurochemestry International, 61,* 1001–1006.

Chinevere, T. D., Sawyer, R. D., Cretzmeyer, A. R., Conlee, R. K., & Parcell, A. C. (2002). Effects of L-tyrosine and carbohydrate ingestion on endurance exercise performance. *Journal of Applied Physiology, 93,* 1590–1597.

Colzato, L. S., De Haan, A., & Hommel, B. (2015). Food for creativity: Tyrosine promotes performance in a convergent-thinking task. *Psychological Research, 79,* 709–714.

Colzato, L. S., Jongkees, B., Sellaro, R., & Hommel, B. (2013). Working memory reloaded: Tyrosine replenishes updating in the N-Back task. *Frontiers in Behavioral Neuroscience, 7,* 200.

Colzato, L. S., Jongkees, B. J., Sellaro, R., van den Wildenberg, W., & Hommel, B. (2014). Eating to stop: Tyrosine supplementation enhances inhibitory control but not response execution. *Neuropsychologia, 62,* 398–402.

Colzato, L. S., Steenbergen, L., Sellaro, R., Stock, A. K., Arning, L., & Beste, C. (2016). Effects of L-Tyrosine on working memory and inhibitory control are determined by DRD2 genotypes: A randomized controlled trial. *Cortex, 82,* 217–224.

Cools, R., & D'Esposito, M. (2011). Inverted-U-shaped dopamine actions on human working memory and cognitive control. *Biological Psychiatry, 69,* 113–125.

Cools, R., Gibbs, S. E., Miyakawa, A., Jagust, W., & D'Esposito, M. (2008). Working memory capacity predicts dopamine synthesis capacity in the human striatum. *Journal of Neuroscience, 28,* 1208–1212.

Cuche, J. L., Prinseau, J., Selz, F., Ruget, G., Tual, J. L., Reingeissen, L., et al. (1985). Oral load of tyrosine or L-DOPA and plasma levels of free and sulfoconjugated catecholamines in healthy men. *Hypertension, 7,* 81–89.

Daubner, S. C., Le, T., & Wang, S. Z. (2011). Tyrosine hydroxylase and regulation of dopamine synthesis. *Archives of Biochemistry and Biophysics, 508,* 1–12.

Deijen, J. B. (2005). Tyrosine. In H. R. Lieberman, R. B. Kanarek, & J. F. Orbleke (Eds.), *Nutrition Brain and Behavior* (pp. 363–381). Boca Raton: CRC Press.

Deijen, J. B., & Orlebeke, J. F. (1994). Effect of tyrosine on cognitive function and blood pressure under stress. *Brain Research Bulletin, 33,* 319–323.

Deijen, J. B., Wientjes, C. J. E., Vullinghs, H. F. M., Cloin, P. A., & Langefeld, J. J. (1999). Tyrosine improves cognitive performance and reduces blood pressure in cadets after one week of a combat training course. *Brain Research Bulletin, 48,* 203–209.

Deutsch, S. I., Rosse, R. B., Schwartz, B. L., Banay-Schwartz, M., McCarthy, M. F., & Johri, S. K. (1994). L-tyrosine pharmacotherapy of schizophrenia: Preliminary data. *Clinical Neuropharmacology, 17,* 53–62.

Fernstrom, J. D. (1990). Aromatic amino acids and monoamine synthesis in the central nervous system: Influence of the diet. *Journal of Nutritional Biochemistry, 1,* 508–517.

Fernstrom, J. D., & Fernstrom, M. H. (2007). Tyrosine, phenylalanine, and catecholamine synthesis and function in the brain. *Journal of Nutrition, 137,* 1539S–1547S.

Foster, H. D., & Hoffer, A. (2004). The two faces of L-DOPA: Benefits and adverse side effects in the treatment of encephalitis lethargica, Parkinson's disease, multiple sclerosis and amyotrophic lateral sclerosis. *Medical Hypotheses, 62,* 177–181.

Gibson, C. J., & Wurtman, R. J. (1977). Physiological control of brain catechol synthesis by brain tyrosine concentration. *Biochemical Pharmacology, 26,* 1137–1142.

Glaeser, B. S., Melamed, E., Growdon, J. H., & Wurtman, R. J. (1979). Elevation of plasma tyrosine after a single oral dose of L-tyrosine. *Life Sciences, 25,* 265–271.

Goldman-Rakic, P. S., Muly, E. C., & Williams, G. V. (2000). D1 receptors in prefrontal cells and circuits. *Brain Research Review, 31,* 295–301.

Jongkees, B. J., Hommel, B., & Colzato, L. S. (2014). People are different: Tyrosine's modulating effect on cognitive control may depend on individual differences related to dopamine function. *Frontiers in Psychology, 5,* 1101.

Jongkees, B. J., Hommel, B., Kühn, S., & Colzato, L. S. (2015). Effect of tyrosine supplementation on clinical populations and healthy populations under stress or cognitive demands: A review. *Journal of Psychiatric Research, 70,* 50–57.

Kvetnansky, R., Sabban, E. L., & Palkovits, M. (2009). Catecholaminergic systems in stress: Structural and molecular genetic approaches. *Physiological Reviews, 89,* 535–606.

Leathwood, P. D., & Pollet, P. (1983). Diet-induced mood changes in normal-populations. *Journal of Psychiatry Research, 17,* 147–154.

Lehnert, H., Reinstein, D. K., Strowbridge, B. W., & Wurtman, R. J. (1984). Neurochemical and behavioral consequences of acute uncontrollable stress: Effects of dietary tyrosine. *Brain Research, 303,* 215–223.

Lieberman, H. R., Corkin, S., Spring, B. J., Growdon, J. H., & Wurtman, R. J. (1983). Mood, performance, and pain sensitivity: Changes induced by food constituents. *Journal of Psychiatry Research, 17,* 135–145.

Lieberman, H. R., Georgelis, J. H., Maher, T. J., & Yeghiayan, S. K. (2005). Tyrosine prevents effects of hyperthermia on behavior and increases norepinephrine. *Physiology & Behavior, 84,* 23–30.

Riggins, J., Pihl, R. O., Benkelfat, C., & Leyton, M. (2012). The dopamine augmenter L-DOPA does not affect positive mood in healthy human volunteers. *PLoS ONE, 7,* e28370.

Magill, R. A., Waters, W. F., Bray, G. A., Volaufova, J., Smith, S. R., Lieberman, H. R., et al. (2003). Effects of tyrosine, phentermine, caffeine D-amphetamine, and placebo on cognitive and motor performance deficits during sleep deprivation. *Nutritional Neuroscience, 6,* 237–246.

Mahoney, C. R., Castellani, J., Kramer, F. M., Young, A., & Lieberman, H. R. (2007). Tyrosine supplementation mitigates memory decrements during cold exposure. *Physiology & Behavior, 92,* 575–582.

Miyake, A., Friedman, N. P., Emerson, M. J., Witzki, A. H., Howerter, A., & Wager, T. D. (2000). The unity and diversity of executive functions and their contributions to complex "frontal lobe" tasks: A latent variable analysis. *Cognitive Psychology, 41,* 49–100.

Moustafa, A. A., Sherman, S. J., & Frank, M. J. (2008). A dopaminergic basis for working memory, learning and attentional shifting in Parkinsonism. *Neuropsychologia, 46,* 3144–3156.

Muly, E. C., III, Szigeti, K., & Goldman-Rakic, P. S. (1998). D1 receptor in interneurons of macaque prefrontal cortex: Distribution and subcellular localization. *Journal of Neuroscience, 18,* 10553–10565.

O'Brien, C., Mahoney, C., Tharion, W. J., Sils, I. V., & Castellani, J. W. (2007). Dietary tyrosine benefits cognitive and psychomotor performance during body cooling. *Physiology & Behavior, 90,* 301–307.

Palinkas, L. A., Reedy, K. R., Smith, M., Anghel, M., Steel, G. D., Reeves, D., et al. (2007). Psychoneuroendocrine effects of combined thyroxine and triiodothyronine versus tyrosine during prolonged antarctic residence. *International Journal of Circumpolar Health, 66,* 401–417.

Rauch, T. M., & Lieberman, H. R. (1990). Tyrosine pretreatment reverses hypothermia-induced behavioral depression. *Brain Research Bulletin, 24,* 147–150.

Shurtleff, D., Thomas, J. R., Ahlers, S. T., & Schrot, J. (1993). Tyrosine ameliorates a cold-induced delayed matching-to-sample performance decrement in rats. *Psychopharmacology (Berl), 112,* 228–232.

Shurtleff, D., Thomas, J. R., Schrot, J., Kowalski, K., & Harford, R. (1994). Tyrosine reverses a cold-induced working-memory deficit in humans. *Pharmacology, Biochemistry and Behavior, 47,* 935–941.

Siessmeier, T., Kienast, T., Wrase, J., Larsen, J. L., Braus, D. F., Smolka, M. N., et al. (2006). Net influx of plasma 6-[F-18]fluoro-L-DOPA (FDOPA) to the ventral striatum correlates with prefrontal processing of affective stimuli. *European Journal of Neuroscience, 24,* 305–313.

Steenbergen, L., Sellaro, R., Hommel, B., & Colzato, L. S. (2015). Tyrosine promotes cognitive flexibility: Evidence from proactive vs. reactive control during task switching performance. *Neuropsychologia, 69,* 50–55.

Sutton, E. E., Coill, M. R., & Deuster, P. A. (2005). Ingestion of tyrosine: Effects on endurance, muscle strength, and anaerobic performance. *International Journal of Sport Nutrition and Exercise Metabolism, 15,* 173–185.

Tam, S. Y., Elsworth, J. D., Bradberry, C. W., & Roth, R. H. (1990). Mesocortical dopamine neurons: High basal firing frequency predicts tyrosine dependence of dopamine synthesis. *Journal of Neural Transmission, 81,* 97–110.

Thomas, J. R., Lockwood, P. A., Sing, A., & Deuster, P. A. (1999). Tyrosine improves working memory in a multitasking environment. *Pharmacology, Biochemistry and Behavior, 64,* 495–500.

Tumilty, L., Davison, G., Beckmann, M., & Thatcher, R. (2011). Oral tyrosine supplementation improves exercise capacity in the heat. *European Journal of Applied Physiology, 111,* 2941–2950.

Tumilty, L., Davison, G., Beckmann, M., & Thatcher, R. (2014). Failure of oral tyrosine supplementation to improve exercise performance in the heat. *Medicine & Science in Sports Exercise, 46,* 1417–1425.

Watson, P., Enever, S., Page, A., Stockwell, J., & Maughan, R. J. (2012). Tyrosine supplementation does not influence the capacity to perform prolonged exercise in a warm environment. *International Journal of Sport Nutrition and Exercise Metabolism, 22,* 363–373.

Wiesel, F. A., Andersson, J. L. R., Westerberg, G., Wieselgren, I. M., Bjerkenstedt, L., Hagenfeldt, L., et al. (1999). Tyrosine transport is regulated differently in patients with schizophrenia. *Schizophrenia Research, 40,* 37–42.

Wurtman, R. J., Hefti, F., & Melamed, E. (1981). Precursor control of neurotransmitter synthesis. *Pharmacological Reviews, 32,* 315–335.

Yeghiayan, S. K., Luo, S. Q., Shukitt-Hale, B., & Lieberman, H. R. (2001). Tyrosine improves behavioral and neurochemical deficits caused by cold exposure. *Physiology & Behavior, 72,* 311–316.

RETRACTED CHAPTER: Tryptophan

Lorenza S. Colzato, Ana Beatriz Rodríguez Moratinos, Martin Reuter and Peter Kirsch

Introduction

Common sense says that "you make a living by what you get but you make a life by what you give." Prosocial behavior has been defined as voluntary acts intended to help or benefit others, for example, by helping or donating (Penner et al. 2005).

Notably, augmented serotonin (5-HT) levels in the brain have been associated to social behaviors like cooperation and affiliation (for reviews see Crockett 2009; Kiser et al. 2012). On the contrary, 5-HT dysfunctions have been observed to be linked with violent criminal, impulsive, and antisocial behaviors (Coccaro et al. 2015).

The original version of this chapter was retracted: The retraction note to this chapter is available at https://doi.org/10.1007/978-3-319-57505-6_24

L.S. Colzato (✉)
Cognitive Psychology Unit and Leiden Institute for Brain and Cognition, Leiden University, Leiden, The Netherlands
e-mail: colzato@fsw.leidenuniv.nl

A.B.R. Moratinos
Departamento de Fisiología, Facultad de Ciencias, Universidad de Extremadura, Badajoz, Spain

M. Reuter
Department of Differential and Biological Psychology, Center for Economics and Neuroscience, University of Bonn, Bonn, Germany

P. Kirsch
Department of Clinical Psychology, Central Institute of Mental Health, Mannheim, Germany

L.S. Colzato
Institute of Cognitive Neuroscience, Faculty of Psychology, Ruhr University Bochum, Bochum, Germany

L.S. Colzato, *Theory-Driven Approaches to Cognitive Enhancement*, https://doi.org/10.1007/978-3-319-57505-6_2

Given the link between social behavior and 5-HT function, it is very plausible that impacting 5-HT levels could result in beneficial changes in prosocial behavior. One way of impacting 5-HT levels is supplementing its chemical forerunner tryptophan (TRP). Given that the human body cannot synthetize TRP itself, TRP is considered an essential amino acid because it is derived from the diet. Interestingly, TRP can augment 5-HT synthesis in rats (Yuwiler 1973) and humans (Bowers 1970). Accordingly, several studies have examined whether the supplementation of TRP can have a positive impact on social behavior that depends on serotonergic function (Crockett 2009; Kiser et al. 2012).

Nonetheless, outcomes from TRP studies have not been completely clear-cut and several factors—such as individual differences—might regulate the effect of TRP on prosocial behavior. In this chapter, adapted from Steenbergen et al. (2016), we will first describe how TRP supplementation impacts 5-HT function. Second, we will outline the available studies on TRP and prosocial behavior. The focus will be on healthy humans with supposedly normal 5-HT levels and not on humans with psychiatric disorders and/or showing antisocial behaviors associated with decreased or dysfunctional 5-HT availability in the brain. The studies in healthy humans point out that TRP has promising potential for promoting social behavior, in particular prosocial and agreeable behavior. Last, we will identify potential modulators of response to TRP supplementation.

Mechanism of Action

TRP plasma levels rise after TRP intake (Yuwiler et al. 1981). The enzyme tryptophan-hydroxylase (TPH), which converts TRP into 5-HT, is accountable for managing the rate at which TRP is transformed into 5-HT (Silber and Schmitt 2010; Young and Gauthier 1981), see also Fig. 1. Notably, the dose of 3 g is enough to saturate TPH and to double the rate of 5-HT synthesis (Young and Gauthier 1981).

On the contrary to other large neutral amino acids (LNAAs) such as valine, leucine, tyrosine, isoleucine, and phenylalanine, TRP is the amino acid that is least abundant in protein (Wu 2009). Therefore, a diet rich in protein will cause reduced increments in TRP plasma levels than in the plasma levels of other LNAAs (for an exhaustive elucidation see Le Floc'h et al. 2011). Additionally, all LNAAs have to be transported through the blood–brain barrier by the same transport system. That is, the LNAAs compete for transport across the blood–brain barrier, which restrains uptake of TRP in the brain (Fernstrom 1990, 2013). Remarkably, as a consequence of this phenomenon, brain TRP and 5-HT levels could actually drop when TRP intake happens together with other LNAAs (Fernstrom and Faller 1978). Nonetheless, the consumption of pure TRP causes a substantial rise in plasma TRP levels and the TRP:LNAA ratio at approximately 60 min after supplementation. Two hours after administration peak plasma and TRP:LNAA levels are obtained after consumption and stay high for at least 7–12 h (Markus et al. 2008; Yuwiler et al. 1981).

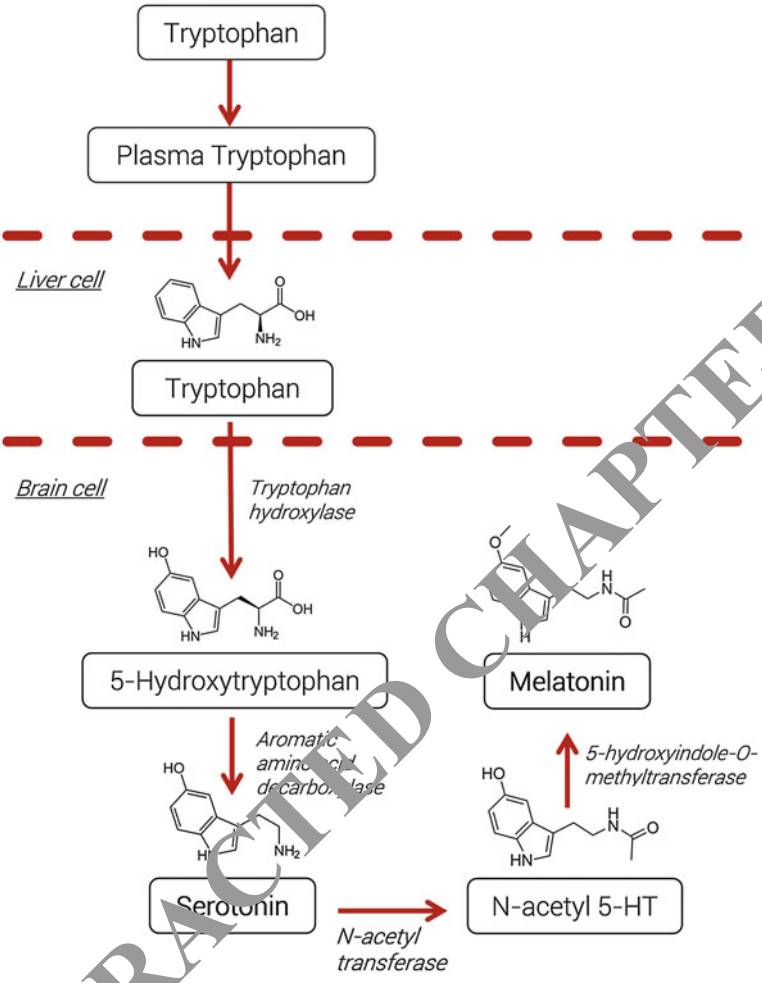


Fig. 1 Schematic representation of the effect of acute tryptophan supplementation on tryptophan to serotonin conversion. Once it has passed the blood–brain barrier, the enzyme tryptophan-hydroxylase converts tryptophan into 5-hydroxytryptophan. In a second step, 5-hydroxytryptophan is converted, via the enzyme aromatic amino acid decarboxylase, into serotonin leading to an elevation in serotonin level. In further steps, serotonin is then converted into melatonin

It has been found that doses up to 5 g of TRP per day do not lead to any harmful effects (Hiratsuka et al. 2013). Only one long-term study, in which the dose of 3 g daily for 3 weeks was supplemented, revealed side-effects (dizziness and epigastric pain) of TRP consumption, even though these conditions were also detected before the start and during the run-in placebo week of the study (Thomson et al. 1982). In contrast, in another long-term study in which 3 g TRP daily was provided to experimental subjects for 12 weeks, only one subject reported diarrhea as a side-effect (Van Praag et al. 1972). The above-mentioned side-effects are more

probable to arise when higher doses are used (i.e., 70–200 mg/kg; for a review see Fernstrom 2012). The amount and diversity of described side-effects increments when higher doses are supplemented over longer periods (e.g., 6 g daily for 3 months; Steinberg et al. 1999). This is not surprising if we consider that TPH enzyme saturates already at a dose up to 3 g (Young and Gauthier 1981), pointing out that doses higher than this will not lead to any further enhancement of 5-HT function. Finally, when TRP is supplemented jointly to drugs known to increase 5-HT functioning such as certain antidepressants, side-effects such as nausea, tremor, dizziness, and drowsiness may occur (Fernstrom 2012).

A dominant hypothesis in explaining the cognitive mechanisms behind the effects of TRP on social behavior in healthy humans relies on the fact that through its impact on the serotonergic system, TRP might induce a selective bias toward positive information. Indeed, enhanced 5-HT levels—obtained via repeated supplementation of TRP or the selective serotonin reuptake inhibitor citalopram—are linked with reduced attentional vigilance toward negative words (Murphy et al. 2006), reduced fear recognition (Harmer et al. 2006), increased recognition of happy faces (Murphy et al. 2006) and increased mood intensity rating (Gibson et al. 2014). However, unfortunately, not every study has confirmed a selective bias toward positive information with high 5-HT. For example, Attenburrow et al. (2003) showed intake of TRP increased the recognition of both happiness and fear. Nonetheless, it seems clear from these studies that TRP administration, alike to antidepressants that enhance 5-HT levels (Harmer 2008), might lead to "positive re-biasing in information processing," causing more attentiveness to positive stimuli. We suggest that such a bias could promote more positive social behaviors such as affiliation and cooperation.

Enhancing Prosocial Behavior in Healthy Humans

The studies in healthy humans described in this section point out to the role of TRP as a promising tool for promoting prosocial behavior. A placebo-controlled study by Aan het Rot et al. (2006) showed that the administration of TRP (1 g, 3 times a day for 15 days) promoted agreeable behavior and perceptions of agreeableness and decreased quarrelsome behavior.

Economic decision-making tasks such as the trust game (Camerer and Weigelt 1988) and the ultimatum game (Güth et al. 1982) have been found to be affected by TRP administration. These economic games include important key processes connected to social behavior such as altruism, empathy, fairness, and cooperation (Ebstein et al. 2010). For example, TRP administration seems to enhance interpersonal trust as indexed by a trust game—a task that measures the extent to which one person (the truster) trusts another person (the trustee), as measured by money units transferred from truster to trustee (Camerer and Weigelt 1988). In agreement with the idea that TRP administration might promote agreeable and prosocial behavior, after the acute intake of 0.8 g TRP, participants transferred significantly

more euros to the trustee than after ingestion of the placebo, an index of augmented interpersonal trust (Colzato et al. 2013). In line with this outcome, charitable donating was enhanced after acute TRP administration (0.8 g). Participants almost doubled the amount of money participants donated to charity, as compared to the placebo condition (Steenbergen et al. 2014).

A recent study by Cerit et al. (2015), in which participants received 2.8 g of TRP or placebo for 6 days, found no significant effect of TRP on behavior in the ultimatum game. In this task, participants are usually asked to make a proposal about the allocation of money among the participant and another player, and/or to accept or reject a proposal by another (sham) participant. The ultimatum game measures the trade-off between decisions driven by fairness versus selfishness. If the proposal is not accepted, both players do not obtain any money. An additional analysis in the study by Cerit et al. (2015), in which seven participants who accepted all offers post-intervention were omitted, pointed out to an increment in rejections of very unfair offers in the TRP group compared the placebo group. As suggested by the authors, this outcome seems to dispute the idea that TRP can enhance prosocial behavior, even though it may be due to the fact that on the testing day TRP has not been administered to the participants. Indeed, according to the authors, this may have lead to a relative depletion as compared to previous days, hence, causing a similar result that one would anticipate as a consequence of TRP depletion (Crockett et al. 2008). Nonetheless, an issue arguing against this possibility is that, within the same study, TRP administration was also found to diminish the physiological response to stress (i.e., reduced cortisol level; for consistent results, see also Cerit et al. 2013). Given that cortisol responses are strongly related to the automatic processing of emotional information (Ellenbogen et al. 2010), with lower cortisol responses indicating less reactivity to stressors, the outcomes by Cerit et al. (2013, 2015) of the lower cortisol response to stressors following TRP, might suggest that TRP supplementation indeed induced a positive bias in information processing. An intriguing alternative interpretation of the outcome that TRP supplementation increased instead of reduced rejection rates is linked to the idea that reciprocity is important for cooperation, which consists of a combination of altruistic rewarding and altruistic punishment (i.e., imposing sanctions on others who violate norms; Fehr and Fischbacher 2003). Hence, if one considers the rejection of unfair offers as an index of altruistic behavior, i.e., altruistic punishment, then an increment of rejections after TRP can in fact reflect a form of prosocial behavior.

Finally, in an unpublished naturalistic pilot study on 292 individuals Peter Kirsch and colleagues at the German central institute of mental health in Mannheim could demonstrate that participants with a TRP rich nutrition regime show better social cognitive performance as measured by the Reading the Mind in the Eyes task.

In sum, these results described above suggest that TRP administration, via augmented 5-HT functioning, has promising potential to promote positive social, i.e., agreeable, prosocial behavior.

TRP Effectivity Depends on Variety of Factors

As pointed out in the Introduction, TRP effects on 5-HT synthesis and functioning seem to rely on several factors, such as the competition between LNAAs (see Section "Mechanism of action"), neuronal activity, enzymatic activity, genetic variability, gender, age and the amount of TRP contained in one's diet (Young 2013). All these factors may contribute in elucidating part of the variability in TRP effectivity, both within and between individuals.

At least in animals, it has been found that the consumption of TRP diminishes the firing rate of serotonergic neurons (Trulson and Jacobs 1976). Notably, this is also the case for the supplementation of selective 5-HT reuptake inhibitors, which are assumed to augment 5-HT availability in the synapse (Fischer et al. 2015). Varying serotonergic levels by means of TRP administration is most likely to modulate the rate of 5-HT release when neurons are firing at a high rate (Trulson and Jacobs 1976). This suggests that effects of TRP supplementation might be most compelling in conditions under which the firing rate of 5-HT neurons is augmented, for example, when exhibiting a high level of behavioral arousal (Young 2013; Young et al. 1988), which, at least in animals, has been shown to regulate the amount of release of 5-HT (Rueter et al. 1997).

Given that TPH enzyme is critical to the conversion of TRP into 5-HT, it is crucial to take into account that this conversion happens in two locations through two different types of enzyme: the gut (TPH1) and the brain (TPH2) (Walther et al. 2003). As 5-HT cannot pass the blood–brain barrier while TRP can, all available 5-HT in the brain relies on the conversion of TRP to 5-HT by TPH2 after TRP has passed the blood–brain barrier. Therefore, if the TPH1 enzyme in the gut is very active, more TRP is converted there and less will be available to pass through the blood–brain barrier and be converted into 5-HT in the brain. Consequently, TRP might have less effect on social behavior in individuals with highly active TPH1 enzyme.

Another factor that increases variability in the effectiveness of TRP supplementation may be vitamin B and D availability. As a matter of fact, activation of the TPH2 enzyme, involved in the first step of the conversion of TRP into 5-HT in the brain (Gutknecht et al. 2009; Walther et al. 2003), relies on vitamin D hormone availability (Haussler et al. 2011). Likewise, the decarboxylase enzyme involved in the last step of the conversion of TRP in 5-HT needs vitamin B6 (pyridoxine) as a cofactor in order to convert 5-HTP into 5-HT. Hence, even though vitamin B6 is not a chemical forerunner of 5-HT, it can be regarded as a rate-limiting factor in the final step of 5-HT synthesis (Deac et al. 2015). To that end, it is frequently advised to take vitamin B and D supplements together with TRP. It is not to exclude that TRP might have decreased effectivity in individuals with deficient vitamin B and D levels.

Moreover, variations in genes linked with serotonergic functioning might play a part in inter-individual variability in response to TRP. Even though the exact role of the A-C polymorphism of the TPH gene in the activity of TPH is unclear, it seems

to play a crucial, functional role. A-carriers (A2051C) have lower levels of 5-HIAA, the main metabolite of 5-HT, as compared to C-carriers (Chen et al. 2010), indicating decreased 5-HT transmission. Furthermore, A-carriers (A218C and A779C) exhibit higher levels of aggression and explicit anger (Hennig et al. 2005; Manuck et al. 1999; Reuter and Hennig 2005). These outcomes point to two opposing hypotheses concerning the potential effect of this polymorphism on TRP effectivity. For once, A-carriers displayed high levels of aggression and explicit anger, indicating much room for enhancement after TRP supplementation. Then again, their decreased 5-HT activity might actually cause less impact of TRP based on the hypothesis that TRP is particularly effective when the firing rate of serotonergic neurons is elevated. At this point, it is not yet clear if and in which direction this polymorphism predicts response to TRP supplementation and more research is needed to answer this question.

Another potential source of TRP effects is inter-subject and intra-sample variability in several factors. For example, variation in body mass index (BMI) might induce different substance concentration levels when the same dose is administered to all participants. Notably, none of the above-discussed studies included individualized dosages. It would be interesting to investigate whether individual differences in TRP effectivity might perhaps be predicted by the individual's BMI. The use of individualized dosages (e.g., a dosage of X mg per kg of bodyweight instead of the same dosage for everyone) might increase the chance to validate consistent and replicable findings with TRP. Furthermore, gender might affect the efficacy of TRP supplementation, since 5-HT synthesis seems to be lower in females than in males (Nishizawa et al. 1997). Along the same line, TRP depletion lowered mood in women but not in men (Ellenbogen et al. 1996). Moreover, age can significantly modulate both serotonergic functioning and (pro)social behavior. For example, aging has been linked to increments in 5-HT availability, receptors, transporters, and enzymes (Fidalgo et al. 2013). Likewise, at least in animals, aging and age-related diseases are linked with unbalanced TRP metabolism (Van der Goot and Nollen 2013).

Finally, we would like to emphasize the importance of baseline levels of social behaviors or related measures. This idea is based on the outcome of Crockett et al. (2010), who found citalopram only modulated moral judgments in those who exhibited higher baseline empathy levels. Considering that one way by which TRP could operate is via the biasing of information processing toward positive stimuli, this implies that in individuals with low 5-HT, the initial bias toward negative stimuli might be greatest and hence they could benefit most from an increase in 5-HT. Nonetheless, support for a relation between TRP efficacy and initial 5-HT state is still controversial (Silber and Schmitt 2010). Connected to the previous issue, substantial research is necessary to explore the possible long-term effects of TRP. This matter is particularly crucial when placebo-controlled within-subjects designs are implemented, as it may help to set the adequate distance between two or more critical sessions.

Conclusion

As the chemical forerunner of 5-HT, TRP has the potential to increase serotonergic function in the brain. TRP seems to be a promising means for promoting prosocial behavior such as agreeableness, sharing, helping, donating in healthy humans. This implies TRP supplementation to be a useful tool to enhance positive social functioning in inexpensive and efficient ways.

TRP, via stimulating 5-HT synthesis, is likely to operate by inducing a positive bias in information processing, causing more attentiveness to positive stimuli and, therefore, less negative (e.g., aggressive), social behavior. It is essential to take into account that, aside from inducing a bias in information processing, the modulating effect of TRP on social behavior might also be mediated by other pathways. For example, TRP supplementation and increments in brain TRP are also related with better quality of sleep and better mood (for a review see Silber and Schmitt 2010), factors which might affect behavior in several ways. The connection between TRP and quality of sleep is very likely if one bears in mind that 5-HT is also the precursor of melatonin, which plays an important role in managing the sleep-wake cycle (Richardson 2005). Moreover, TRP is regarded to have a mild sedative effect, possibly due to the increment in melatonin production linked with the rise in 5-HT levels (Bravo et al. 2012). Such a connection may elucidate, for instance, the beneficial effects that TRP can have on impulsive behavior (Silber and Schmitt 2010).

The link between TRP and mood may illustrate an alternative pathway via which TRP can modulate social behavior. As suggested by Young (2013), given that increments in 5-HT may have beneficial effects on mood (Bravo et al. 2013), and as better mood is typically linked to more positive social interactions, the effects of TRP in enhancing prosocial behavior may just be the results of better mood following TRP ingestion.

Another important aspect regards the fact that TRP can be metabolized not only via the 5-HT pathway but also via the kynurenine pathway. As pointed out by Steenbergen et al. (2016), De facto, outside the central nervous system, only one percent of dietary TRP is converted into 5-HT. This means that the majority of TRP is catabolized along the kynurenine pathway (Russo et al. 2003). In the first step of this metabolic way, TRP is transformed into kynurenine. Subsequently, kynurenine is converted to a series of metabolites, such as 3-hydroxykynurenine and quinolinic acid (for a detailed explanation of this oxidative pathway, see Russo et al. 2003). Notably, kynurenine can pass the blood–brain barrier and prompt the production of neuroactive metabolites that affect glutamatergic and cholinergic signaling. This fact indicates that TRP effects are not modulated solely by 5-HT. This might be specifically relevant for females afflicted by irritable bowel syndrome, as they show an increase of TRP catabolism along the kynurenine pathway, which contributes to the abnormal 5-HT functioning in this syndrome (Fitzgerald et al. 2008). Therefore, considering individual differences in TRP metabolism (e.g., the amount of TRP metabolized via the kynurenine pathway vs. via the 5-HT pathway) may offer important understandings into the effectivity of TRP in modulating social behavior.

In sum, even though more research is needed to disentangle and understand the relation between individual differences, TRP effectivity, 5-HT functioning, and social interactions, we suggest that TRP can be an effective tool in enhancing prosocial behavior in healthy humans.

Acknowledgements This work was supported by a research grant from the *Joint Programming Initiative (JPI): A healthy diet for a healthy life* awarded to the authors (#529051004).

References

Aan het Rot, M., Moskowitz, D. S., Pinard, G., & Young, S. N. (2006). Social behaviour and mood in everyday life: The effects of tryptophan in quarrelsome individuals. *Journal of Psychiatry and Neuroscience, 31*(4), 253–262.

Attenburrow, M. J., Williams, C., Odontiadis, J., Reed, A., Powell, J., Cowen, P. J., et al. (2003). Acute administration of nutritionally sourced tryptophan increases face recognition. *Psychopharmacology (Berl), 169*(1), 104–107.

Bowers, M. B., Jr. (1970). Cerebrospinal fluid 5-hydroxyindoles and behavior after L-tryptophan and pyridoxine administration to psychiatric patients. *Neuropharmacology, 9*(6), 599–604.

Bravo, R., Matito, S., Cubero, J., Franco, L., Sánchez, C., Rodríguez, A. B., … Barriga, C. (2012). Assessment of the intake of tryptophan-enriched cereals in the elderly and its influence on the sleep-wake circadian rhythm. *Antropologia Portuguesa, 29*, 113–120.

Bravo, R., Matito, S., Cubero, J., Paredes, S. D., Franco, L., Rivero, M., … Barriga, C. (2013). Tryptophan-enriched cereal intake improves nocturnal sleep, melatonin, serotonin, and total antioxidant capacity levels and mood in elderly humans. *Age, 35*(4), 1277–1285.

Camerer, C., & Weigelt, K. (1988). Experimental tests of a sequential equilibrium reputation model. *Econometrica: Journal of Econometric Society, 56*(1), 1–36.

Cerit, H., Jans, L. A., & Van der Does, A. J. W. (2013). The effect of tryptophan on the cortisol response to social stress is moderated by the 5-HTTLPR. *Psychoneuroendocrinology, 38*(2), 201–208.

Cerit, H., Schuur, R. J., De Bruijn, E. R. A., & Van der Does, A. J. W. (2015). Tryptophan supplementation and the response to unfairness in healthy volunteers. *Frontiers in Psychology, 6,* 1012.

Chen, G. L., Novak, M. A., Meyer, J. S., Kelly, B. J., Vallender, E. J., & Miller, G. M. (2010). The effect of rearing experience and TPH2 genotype on HPA axis function and aggression in rhesus monkeys: A retrospective analysis. *Hormones and Behavior, 57*(2), 184–191.

Coccaro, E. F., Fanning, J. R., Phan, K. L., & Lee, R. (2015). Serotonin and impulsive aggression. *CNS Spectrums, 20*(3), 295–302.

Colzato, L. S., Steenbergen, L., de Kwaadsteniet, E. W., Sellaro, R., Liepelt, R., & Hommel, B. (2015). Tryptophan promotes interpersonal trust. *Psychological Science, 24*(12), 2575–2577.

Crockett, M. J. (2009). The neurochemistry of fairness. *Annals of the New York Academy of Science, 1167,* 76–86.

Crockett, M. J., Clark, L., Hauser, M. D., & Robbins, T. W. (2010). Serotonin selectively influences moral judgment and behavior through effects on harm aversion. *Proceedings of the National Academy of Science, 107*(40), 17433–17438.

Crockett, M. J., Clark, L., Tabibnia, G., Lieberman, M. D., & Robbins, T. W. (2008). Serotonin modulates behavioral reactions to unfairness. *Science, 320*(5884), 1739.

Deac, O. M., Mills, J. L., Shane, B., Midttun, Ø., Ueland, P. M., Brosnan, J. T., … Molloy, A. M. (2015). Tryptophan catabolism and vitamin b-6 status are affected by gender and lifestyle factors in healthy young adults. *Journal of Nutrition, 145*(4), 701–707.

Ebstein, R. P., Israel, S., Chew, S. H., Zhong, S., & Knafo, A. (2010). Genetics of human social behavior. *Neuron, 65*(6), 831–844.

Ellenbogen, M. A., Carson, R. J., & Pishva, R. (2010). Automatic emotional information processing and the cortisol response to acute psychosocial stress. *Cognitive, Affective, & Behavioral Neuroscience, 10*(1), 71–82.

Ellenbogen, M. A., Young, S. N., Dean, P., Palmour, R. M., & Benkelfat, C. (1996). Mood response to acute tryptophan depletion in healthy volunteers: Sex differences and temporal stability. *Neuropsychopharmacology, 15*(5), 465–474.

Fehr, E., & Fischbacher, U. (2003). The nature of human altruism. *Nature, 425,* 785–791.

Fernstrom, J. D. (1990). Aromatic amino acids and monoamine synthesis in the central nervous system: Influence of the diet. *The Journal of Nutritional Biochemistry, 1*(10), 508–517.

Fernstrom, J. D. (2012). Effects and side effects associated with the non-nutritional use of tryptophan by humans. *Journal of Nutrition, 142*(12), 2236–2244.

Fernstrom, J. D. (2013). Large neutral amino acids: Dietary effects on brain neurochemistry and function. *Amino Acids, 45*(3), 419–430.

Fernstrom, J. D., & Faller, D. V. (1978). Neutral amino acids in the brain: Changes in response to food ingestion. *Journal of Neurochemistry, 30*(6), 1531–1538.

Fidalgo, S., Ivanov, D. K., & Wood, S. H. (2013). Serotonin: From top to bottom. *Biogerontology, 14*(1), 21–45.

Fischer, A. G., Jocham, G., & Ullsperger, M. (2015). Dual serotonergic signals: A key to understanding paradoxical effects? *Trends in Cognitive Sciences, 19*(1), 21–26.

Fitzgerald, P., Cassidy E. M., Clarke, G., Scully, P., Barry, S., Quigley, E. M. M., … Dinan, T. G. (2008). Tryptophan catabolism in females with irritable bowel syndrome: Relationship to interferon-gamma, severity of symptoms and psychiatric co-morbidity. *Neurogastroenterology and Motility, 20*(12), 1291–1297.

Gibson, E. L., Vargas, K., Hogan, E., Holmes, A., Rogers, P. J., Witteveen, J., … Mohajeri, M. H. (2014). Effects of acute treatment with a tryptophan-rich protein hydrolysate on plasma amino acids, mood and emotional functioning in older women. *Psychopharmacology, 231*(24), 4595–4610.

Güth, W., Schmittberger, R., & Schwarze, B. (1982). An experimental analysis of ultimatum bargaining. *Journal of Economic Behavior & Organization, 3*(4), 367–388.

Gutknecht, L., Kriegebaum, C., Waider, J., Schmitt, A., & Lesch, K. P. (2009). Spatio-temporal expression of tryptophan hydroxylase isoforms in murine and human brain: Convergent data from Tph2 knockout mice. *European Neuropsychopharmacology, 19*(4), 266–282.

Harmer, C. J. (2008). Serotonin and emotional processing: Does it help explain antidepressant drug action? *Neuropharmacology, 55*(6), 1023–1028.

Harmer, C. J., Mackay, C. E., Reid, C. B., Cowen, P. J., & Goodwin, G. M. (2006). Antidepressant drug treatment modulates the neural processing of nonconscious threat cues. *Biological Psychiatry, 59*(9), 816–820.

Haussler, M. R., Jurutka, P. W., Mizwicki, M., & Norman, A. W. (2011). Vitamin D receptor (VDR)-mediated actions of 1α, 25 (OH) 2 vitamin D 3: Genomic and non-genomic mechanisms. *Best Practice & Research Clinical Endocrinology & Metabolism, 25*(4), 543–559.

Hennig, J., Reuter, M., Netter, P., Burk, C., & Landt, O. (2005). Two types of aggression are differentially related to serotonergic activity and the A779C TPH polymorphism. *Behavioral Neuroscience, 119*(1), 16–25.

Hirotsuka, C., Fukuwatari, T., Sano, M., Saito, K., Sasaki, S., & Shibata, K. (2013). Supplementing healthy women with up to 5.0 g/d of L-tryptophan has no adverse effects. *Journal of Nutrition, 143*(6), 859–866.

Kiser, D., Steemer, S. B., Branchi, I., & Homberg, J. R. (2012). The reciprocal interaction between serotonin and social behaviour. *Neuroscience and Biobehavioral Reviews, 36*(2), 786–798.

Le Floc'h, N., Otten, W., & Merlot, E. (2011). Tryptophan metabolism, from nutrition to potential therapeutic applications. *Amino Acids, 41*(5), 1195–1205.

Manuck, S. B., Flory, J. D., Ferrell, R. E., Dent, K. M., Mann, J. J., & Muldoon, M. F. (1999). Aggression and anger-related traits associated with a polymorphism of the tryptophan hydroxylase gene. *Biological Psychiatry, 45*(5), 603–614.

Markus, C. R., Firk, C., Gerhardt, C., Kloek, J., & Smolders, G. F. (2008). Effect of different tryptophan sources on amino acids availability to the brain and mood in healthy volunteers. *Psychopharmacology (Berl), 201*(1), 107–114.

Murphy, S. E., Longhitano, C., Ayres, R. E., Cowen, P. J., & Harmer, C. J. (2006). Tryptophan supplementation induces a positive bias in the processing of emotional material in healthy female volunteers. *Psychopharmacology (Berl), 187*(1), 121–130.

Nishizawa, S., Benkelfat, C., Young, S. N., Leyton, M., Mzengeza, S. D., De Montigny, C., … Diksic, M. (1997). Differences between males and females in rates of serotonin synthesis in human brain. *Proceedings of the National Academy of Science, 94*(10), 5308–5313.

Penner, L. A., Dovidio, J. F., Piliavin, J. A., & Schroeder, D. A. (2005). Prosocial behaviour: Multilevel perspectives. *Annual Review of Psychology, 56,* 365–392.

Reuter, M., & Hennig, J. (2005). Pleiotropic effect of the TPH A779C polymorphism on nicotine dependence and personality. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics, 134*(1), 20–24.

Richardson, G. S. (2005). The human circadian system in normal and disordered sleep. *Journal of Clinical Psychiatry, 66,* 3–9.

Rueter, L. E., Fornal, C. A., & Jacobs, B. L. (1997). A critical review of 5-HT brain microdialysis and behaviour. *Reviews in the Neurosciences, 8*(2), 117–138.

Russo, S., Kema, I. P., Fokkema, R. M., Boon, J. C., Willemse, P. H., de Vries, E. G., … Korf, J. (2003). Tryptophan as a link between psychopathology and somatic states. *Psychosomatic Medicine, 65*(4), 665–671.

Silber, B. Y., & Schmitt, J. A. (2010). Effects of tryptophan loading on human cognition, mood, and sleep. *Neuroscience and Biobehavioral Reviews, 34*(3), 387–407.

Steenbergen, L., Jongkees, B., Sellaro, R., & Colzato, L. S. (2015). Tryptophan supplementation modulates social behavior: A review. *Neuroscience and Biobehavioral Reviews, 64,* 346–358.

Steenbergen, L., Sellaro, R., & Colzato, L. S. (2014). Tryptophan promotes charitable donating. *Frontiers in Psychology, 5,* 1451.

Steinberg, S., Annable, L., Young, S. N., & Liquornik, N. (1999). A placebo-controlled clinical trial of L-tryptophan in premenstrual dysphoria. *Biological Psychiatry, 45*(3), 313–320.

Thomson, J., Rankin, H., Ashcroft, G., Yates, C., McQueen, J., & Cummings, S. (1982). The treatment of depression in general practice. A comparison of L-tryptophan, amitriptyline, and a combination of L-Tryptophan and Amitriptyline with placebo. *Psychological Medicine, 12*(4), 741–751.

Trulson, M. E., & Jacobs, B. L. (1976). Dose-response relationships between systemically administered L-tryptophan or L-5-hydroxytryptophan and raphe unit activity in the rat. *Neuropharmacology, 15*(6), 339–344.

Van der Goot, A. T., & Nollen, E. A. (2013). Tryptophan metabolism: Entering the field of aging and age-related pathologies. *Trends in Molecular Medicine, 19*(6), 336–344.

Van Praag, H. M., Korf, J., Dols, L. C. W., & Schut, T. (1972). A pilot study of the predictive value of the probenecid test in application of 5-Hydroxytryptophan as antidepressant. *Psychopharmacology (Berl), 25*(1), 14–21.

Walther, D. J., Peter, J. U., Bashammakh, S., Hörtnagl, H., Voits, M., Fink, H., et al. (2003). Synthesis of serotonin by a second tryptophan hydroxylase isoform. *Science, 299*(5603), 76.

Wu, G. (2009). Amino acids: Metabolism, functions, and nutrition. *Amino Acids, 37*(1), 1–17.

Young, S. N. (2013). The effect of raising and lowering tryptophan levels on human mood and social behaviour. *Philosophical Transactions of the Royal Society B: Biological Science, 368* (1615), 20110375.

Young, S. N., & Gauthier, S. (1981). Tryptophan availability and the control of 5-hydroxytryptamine and tryptamine synthesis in human CNS. *Advances in Experimental Medicine and Biology, 133,* 221–230.

Young, S. N., Pihl, R. O., & Ervin, F. R. (1988). The effect of altered tryptophan levels on mood and behavior in normal human males. *Clinical Neuropharmacology, 11,* S207–S215.

Yuwiler, A. (1973). Conversion of D-and L-tryptophan to brain serotonin and 5-hydroxyindoleacetic acid and to blood serotonin1. *Journal of Neurochemistry, 20*(4), 1099–1109.

Yuwiler, A., Brammer, G. L., Morley, J. E., Raleigh, M. J., Flannery, J. W., & Geller, E. (1981). Short-term and repetitive administration of oral tryptophan in normal men: Effects on blood tryptophan, serotonin, and kynurenine concentrations. *Archives of General Psychiatry, 38*(6), 619–626.


choline
CHOLINE
500MG

Choline

Lorenza S. Colzato, Katrin Schlauch,
Janna Katharina Kullmann and Tamara Wild

Introduction

The amino acid choline is a biochemical precursor of phospholipids and sphingomyelin, which are essential components of all membranes, especially necessary for the structural integrity and signaling functions of cell membranes (Howe et al. 2004; Zeisel et al. 1991). It is also a precursor of acetylcholine (ACh) (Zeisel et al. 1991). ACh is a major neurochemical of the central and peripheral nervous system involved in learning and memory processes (Hasselmo 2006). Choline supplementation increases choline blood plasma concentration and subsequently inter-neuronal choline brain concentration. This increase may accelerate ACh synthesis (Batool et al. 2016; Cohen and Wurtman 1975). Given that choline can enhance choline metabolites in the human brain (Babb et al. 2004), several studies investigated the effectiveness of choline supplementation as a tool to promote cognitive abilities, especially in the clinical domain (for reviews see Leermakers et al. 2015; Parnetti et al. 2007). Unfortunately, reports on the effects of choline supplementation on cognition in healthy humans are quite sparse and inconsistent. The aim of this chapter is to provide a summary of the available studies on the

L.S. Colzato (✉)
Cognitive Psychology Unit and Leiden Institute for Brain and Cognition, Leiden University, Leiden, The Netherlands
e-mail: colzato@fsw.leidenuniv.nl

K. Schlauch · J.K. Kullmann · T. Wild
Institute of Experimental Psychology, Heinrich-Heine University, Düsseldorf, Germany

L.S. Colzato
Institute of Cognitive Neuroscience, Faculty of Psychology, Ruhr University Bochum, Bochum, Germany

L.S. Colzato, *Theory-Driven Approaches to Cognitive Enhancement*,
DOI 10.1007/978-3-319-57505-6_3

effects of choline supplementation on cognition in healthy humans in order to better understand under which circumstances choline has a positive effect and to clarify whether choline can act as a useful cognitive enhancer.

In this chapter, we will first describe how choline supplementation affects ACh function. Second, we will outline the available studies investigating a long-term diet rich in choline across the life span. Third, we will review studies exploring the short-term effect of choline supplementation on various cognitive processes. The studies indicate that choline has the potential to enhance in particular memory processes in low-performing individuals, suggesting an inverted u-shaped pattern of effectivity.

Mechanism of Action

Acetylcholine is synthesized from choline and acetyl coenzyme A in a reaction that is catalyzed by the enzyme choline acetyltransferase (Wu and Hersh 1994; Zeisel and Blusztajn 1994). The administration of choline can cause sequential increases in choline and ACh concentrations in rats. Choline uptake peaks approximately 30 min after ingestion and ACh levels in the brain significantly rise after about 40 min and remain high for around 90 min (Cohen and Wurtman 1975; Haubrich et al. 1975). This increase in ACh concentration is dose dependent between 15 and 60 mg/kg. Higher doses of choline do not lead to higher increments in ACh concentration (Cohen and Wurtman 1975). These outcomes indicate that precursor availability may affect brain ACh synthesis similar to how brain tyrosine and tryptophan levels have been previously found to regulate the syntheses of brain dopamine and serotonin (see Chapters "Tyrosine" and "Tryptophan" on tyrosine and tryptophan). Hence, an increase in plasma choline is not a sufficient condition for increased ACh synthesis. It seems that increased plasma choline enhances cholinergic function to the extent that cholinergic neurons are activated simultaneously with choline treatment or as a consequence of ACh depletion (Jope 1982; Trommer et al. 1982). After ingestion, choline is transported across the blood–brain barrier by a bidirectional and unsaturated carrier mechanism (Cornford et al. 1978; Lockman and Allen 2002). This mechanism transports choline at a rate proportional to serum choline concentration. That is, when the blood choline concentration increases so does the brain choline concentration (Lockman and Allen 2002). Effects of choline on ACh synthesis mainly occur because of the enzyme choline acetyltransferase, which is involved in the first step of the synthesis of choline into ACh and responsible for regulating at which rate choline is converted into ACh (Ueland 2011), see Fig. 1. The activity of the enzyme choline acetyltransferase is affected by several factors like precursor availability, feedback inhibition by its end-products, and the individual variability in the activity of high-affinity uptake of choline (Zeisel 1981).

Given that choline is an essential amino acid, the body cannot synthesize it in a sufficient amount by itself (Zeisel and Blusztajn 1994). Accordingly, it is crucial to ingest food that contains a certain amount of choline (Zeisel 1981). The Institute of Medicine and National Academy of Sciences USA recommended an adequate

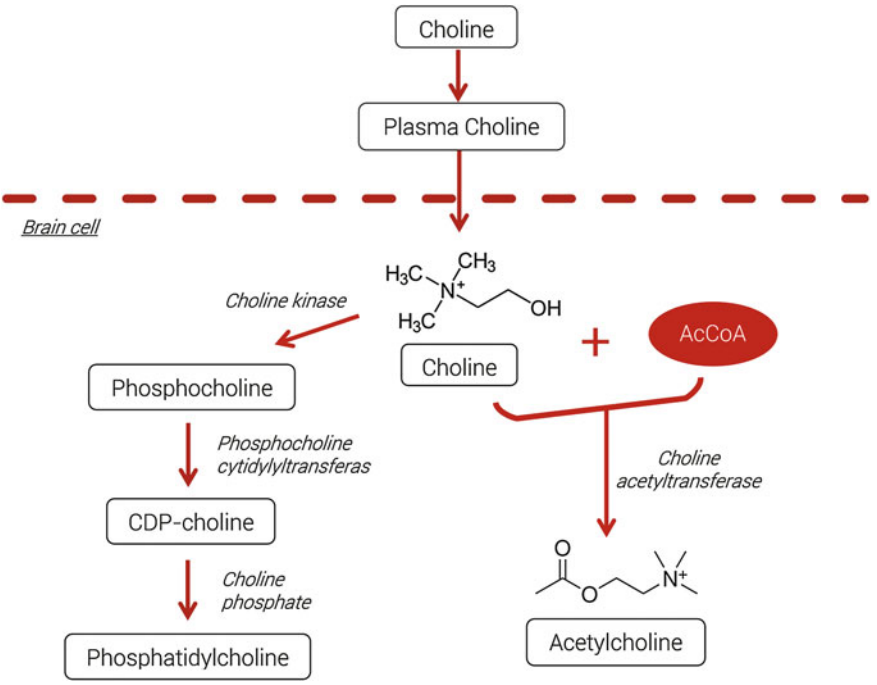


Fig. 1 Schematic representation of the effect of acute choline supplementation on choline to acetylcholine conversion. Once it has passed the blood–brain barrier, the acetyl coenzyme A (AcCoA) and the enzyme choline acetyltransferase convert choline into acetylcholine leading to an elevation in acetylcholine level. In another series of reactions choline, via several steps, is synthesized to phosphatidylcholine, a phospholipid that incorporates choline as a headgroup

intake for choline of 550 mg/day for men and 425 mg/day for women, with a higher recommended intake during pregnancy and lactation (Yates et al. 1998). Choline and esters of choline can be ingested through protein-rich food. The highest total choline concentrations (mg/100 g) are contained in beef liver (418 mg), chicken liver (290 mg), and eggs (251 mg). But also fish, milk, as well as several plant foods like certain beans or nuts are a good source of choline (Howe et al. 2004; Zeisel et al. 2003). The established recommended upper intake level for adults is 3.5 g (Food and nutrition board of the US—Institute of Medicine). The ingestion of high choline doses (e.g., >5 g/day) can produce side effects such as sweating, nausea, vomiting, bloating, and diarrhea.

Choline at Long-Term: Enhancement Across the Life Span

Across the life span a diet rich in choline seems to exert neuroprotective functions and to enhance cognition. In this section, we will give an overview about recent findings involving long-term studies on this topic. Several animal studies suggest

that a diet rich in choline leads to positive outcomes in the offspring. For instance, the offspring of rat dams showed better memory function when they were exposed to higher levels of choline in utero (Williams et al. 1998). Boeke et al. (2013) demonstrated that choline intake during pregnancy also affects visuospatial memory in humans. In this study the researchers assessed the amount of choline intake of 1896 pregnant women with high socioeconomic backgrounds by means of the 130-item semi-quantitative food frequency questionnaire as well as a 33-item detailed interview about the usage of nutritional supplements. At age 7, children were approached and asked to perform cognitive tests to assess visuospatial memory (Wide Range Assessment of Memory and Learning, Design and Picture Memory subtests; WRAML2), and verbal and nonverbal intelligence (Kaufman Brief Intelligence Test, Second Edition; KBIT-2). Results showed that a diet rich in choline during the second trimester, and to a smaller extent also in the first trimester, was linked to better visuospatial memory at age 7, as measured by the WRAML2 Design and Picture Memory subtests. Moreover, a positive correlation between second-trimester choline intake and nonverbal intelligence has been found. The researchers suggested that the beneficial effects of maternal gestational choline ingestion on the children were due to enhanced brain function via the modulation of cholinergic transmission or epigenetics changes in the myelination of neurons. On the other hand, another study could not replicate this outcome. A randomized, double-blind, placebo-controlled trial did not show an enhancement of infant cognitive functions when pregnant women, who were consuming moderate-choline diets, were supplemented with phosphatidylcholine (a class of phospholipids that incorporate choline as a headgroup) (Cheatham et al. 2012). The discrepancy in the results of these two studies may be due to the different samples in terms of socioeconomic status of women investigated. It may be that the lower socioeconomic status and associated unfavorable environmental conditions overshadowed the efficacy of choline supplementation. This idea would also be in line with another study in which participants from a disadvantaged background (Signore et al. 2008) showed no association between serum choline and child IQ score. Unfortunately, it is plausible to assume that a diet rich in choline cannot compensate for unfavorable environmental factors. However, a study by Jiang et al. (2012) underlines the beneficial effect of ingesting choline during pregnancy. Twenty-four women in the third trimester of pregnancy either consumed 480 or 930 mg choline per day. Researchers collected maternal and placental blood samples as well as samples of placental tissue. Women who were administered more choline, had lower levels of cortisol in the placental cord and changes in cortisol-regulating genes in both the placental and fetal tissue. The authors concluded that choline supplementation during pregnancy might counteract the adverse effects of prenatal stress. This finding may be particularly relevant for women who experience considerable amount of stress during their pregnancy and might want to enhance the neuroendocrine and metabolic development of their offspring.

The intake of choline seems not only to be beneficial in prenatal and postnatal cognitive enhancement in young children, but also to compensate for cognitive decline in healthy elderly. Given that during the course of normal aging a reduction

in phospholipid phosphatidylcholine takes place (Roth et al. 1995; Rouser and Yamamoto 1968), Babb et al. (2002) investigated with a proton decoupled P-MRS technique whether chronic citicoline (intermediate product of phosphatidylcholine) intake could increase phospholipid phosphatidylcholine and further enhance cognition. Elderly volunteers were scanned and neurologically assessed before and after taking 500 mg citicoline every day over the course of 6 weeks. In addition to the measurable increases in phospholipid phosphatidylcholine, a correlation between this increase and improved verbal memory was established. The authors conclude that choline supplementation might have neuroprotective properties in aging adults, preserving learning, and memory abilities (Babb et al. 2002). Consistent with the aforementioned result, Spiers et al. (1996) explored in a randomized, double-blind, placebo-controlled study the effects of citicoline on verbal memory in elderly mentally healthy adults. The volunteers received a placebo or citicoline, 1000 mg/day, for 3 months. For the crossover study, the low-performing individuals were tested again. This time the subjects took both placebo and citicoline, 2000 mg/day, each for 2 months. It was found that citicoline therapy promoted delayed recall on logical memory only for the subjects with relatively low-functioning memories. The higher dosage of citicoline was linked to improved immediate and delayed logical memory. Hence the authors suggested that citicoline therapy improves verbal memory functioning in healthy older individuals with relatively low-functioning memory. Furthermore, Poly et al. (2011) conducted in a community-based population of 1391 healthy, nondemented individuals between 36 and 83 years of age, a longitudinal study to explore the association between choline intake and cognitive outcome measures. At two time points (1991–1995 and 1998–2001), daily choline intake was measured by means of the Harvard Food Frequency Questionnaire. At the second test point, structural imaging measures and four neuropsychological factors were assessed in addition to the food questionnaire: verbal memory, visual memory, verbal learning, and executive function. Higher concurrent choline intake was associated with better verbal memory and visual memory performance, whereas higher remote choline intake, on the other hand, was linked to smaller white matter hyperintensity. The fact that choline intake is related to white matter hyperintensity suggests that choline intake at midlife may be neuroprotective. Likewise, in an extensive cross-sectional study by Nurk et al. (2013) the association between plasma free choline, betaine, and cognitive functioning in a sample of 2195 healthy elderly participants was examined. A low plasma concentration of free choline was associated with poor performance in global cognition, sensorimotor speed, perceptual speed, and executive function (Nurk et al. 2013). However, Eussen et al. (2007) did not find an association of plasma choline with cognitive function and argued that plasma choline might be a poor marker for the effects choline exerts on the brain (Eussen et al. 2007).

In sum, the long-term intake of choline seems to show promising potential to enhance certain memory functions across the life span: to achieve prenatal and postnatal cognitive enhancement in young children and to compensate for cognitive decline in aging.

Choline at Short-Term: Enhancement in Healthy Adults

In this section, the few studies investigating the effect of short-term choline supplementation on several cognitive functions will be reviewed.

In a placebo-controlled study, Naber et al. (2015) reported improved visuomotor performance in healthy adults after the ingestion of 3 g choline bitartrate administered 70–90 min before testing. The authors suggested that choline administration is able to shift the speed-accuracy trade-off of actions toward accuracy, and thus leads to an improved spatial coordination. Moreover, a decrement in pupil size was found, indicating possible changes in the autonomous nervous system induced by the cholinergic modulation of attention (Naber et al. 2015). Further, in a study by Deuster (2002), cognitive and physical performance was assessed after participants received either two doses of 25 mg/kg choline supplementation or a placebo 30 min before and 60 min after an extensive load carrying exercise task. Whereas Naber et al. (2015) found changes in spatial coordination and attention, an increase in plasma choline did not lead to changes in physical performance nor in reaction time, logical reasoning, vigilance, spatial memory, or working memory (Deuster 2002). The discrepancy between the two studies in physical performance may be explained by the fact that choline supplementation is more likely to affect fine-motor control rather than ballistic movements (Nag and Berger-Sweeney 2007). The null-findings in the cognitive domain by Deuster (2002) may be due by failing to take into account individual differences (i.e., low vs. high performers). Notably, in another study enhancing effects on processing speed, working memory, verbal learning, verbal memory, and executive function were only observable in low-performing individuals (Knott et al. 2015a). In a randomized, double-blind, crossover design by Knott et al. (2015a) participants were given a placebo, a single low (500 mg) or moderate (1000 mg) dose of CDP-choline. Four hours after ingestion they were asked to complete the CogState Schizophrenia Battery, used to detect cognitive changes (Falleti et al. 2006), in each of the three test sessions. CDP-choline supplementation was found to enhance cognitive performance of the low achieving individuals but impair performance in moderately efficient and high cognitive task performers. Likewise, in a double-blind counterbalanced study by Ladd et al. (1993) a trend to greater enhancement in slow learners was observed. Healthy subjects, after having received either a dose of 25, 10 g phosphatidylcholine or a placebo, had to complete a serial learning task 60 or 90 min after ingestion. After intake of 25 g phosphatidylcholine a significant enhancement of explicit memory after 90 min and a moderate enhancement after 60 min was found, but not for remote, semantic, or implicit memory. Along the same line, Sitaram et al. (1978) showed that the supplementation of choline significantly enhanced serial learning in healthy adults and that "poor" performers were more receptive to the enhancing effects after the administration. This series of outcomes suggest that compared to high, low-performing individuals might profit the most from choline supplementation. An explanation for this pattern of results might be that choline supplementation follows an inverted u-shaped pattern of effectivity (Bentley et al.

2011). That is, for high performing individuals who already possess an optimal cholinergic state, choline supplementation might lead to a hyper-cholinergic supraoptimal state, decreasing cognitive performance. In contrast, for low performing individuals who instead possess a suboptimal cholinergic state, choline supplementation, by filling the cholinergic supply, might lead to improved cholinergic stimulation and enhanced cognitive performance. Accordingly, choline may exert protective and enhancing properties only in individuals associated to a low cholinergic baseline levels (Knott et al. 2015a).

All in all, these results suggest that short-term choline supplementation can enhance cognition in healthy adults. However, the positive effects are restricted to certain cognitive domains, like visual and verbal episodic memory and visuomotor abilities. Furthermore, individuals with low choline baseline levels in the brain are likely to profit the most from the supplementation.

Conclusion

As the biochemical precursor of ACh, choline has the potential to enhance cholinergic metabolism in the brain. Although more research is needed to explain contradictory results and to fully understand the effects choline exerts on cognition in healthy humans, a long-term diet rich in choline seems to enhance cognitive functioning across the life span. Besides leading to prenatal and postnatal cognitive enhancement in young child, choline might exert neuroprotective functions in normal aging given that a diet rich in choline was associated with lower white matter hyperintensities, which is associated with decreased risk of stroke, dementia, and premature death (Poly et al. 2011).

At short-term, choline supplementation seems to have the potential to enhance various cognitive processes (in particular memory), especially in poor performers. Low performing individuals might profit the most from choline supplementation, because of an inverted u-shaped pattern of choline effectivity on cognitive performance. Accordingly, future studies investigating the effect of choline on cognition should mandatorily take into account individual difference in performance (low vs. high performers) and genetic markers associated with ACh availability in the brain. Indeed, genetic carriers associated with low ACh baseline levels are the ones expected to profit the most from the choline intervention. Hence, we suggest that genetic predisposition might modulate the effect of choline in its role as cognitive enhancer.

Future studies need to shed light on the neurological underpinnings underlying the cognitive enhancement effects induced by choline. Notably, Knott et al. (2015b) showed dose-dependent effects of choline supplementation on resting state brain oscillations. Spectral analysis exhibited dose-dependent declines in delta and increments in alpha oscillations, which were also accompanied by decrements in beta and gamma oscillatory activity. As pointed out by the authors, these outcomes

sustain the idea that choline-induced cognitive enhancement implicates multiple mechanisms including facilitated nicotinic cholinergic action.

In sum, even if more research is necessary, we can conclude that choline is a promising tool for enhancing in particular memory functions in low-performing individuals and might exert neuroprotective functions across the life span.

References

Babb, S. M., Ke, Y., Lange, N., Kaufman, M. J., Renshaw, P. F., & Cohen, B. M. (2004). Oral choline increases choline metabolites in human brain. *Psychiatry Research Neuroimaging, 130*(1), 1–9.

Babb, S., Wald, L., Cohen, B., Villafuerte, R., Gruber, S., Yurgelun-Todd, D., et al. (2002). Chronic citicoline increases phosphodiesters in the brains of healthy older subjects: An in vivo phosphorus magnetic resonance spectroscopy study. *Psychopharmacology (Berl), 161*(3), 248–254.

Batool, Z., Sadir, S., Liaquat, L., Tabassum, S., Madiha, S., Rafiq, S., … Naqvi, F. (2016). Repeated administration of almonds increases brain acetylcholine levels and enhances memory function in healthy rats while attenuates memory deficits in animal model of amnesia. *Brain Research Bulletin, 120*, 63–74.

Bentley, P., Driver, J., & Dolan, R. J. (2011). Cholinergic modulation of cognition: Insights from human pharmacological functional neuroimaging. *Progress in Neurobiology, 94*(4), 360–388.

Boeke, C. E., Gillman, M. W., Hughes, M. D., Rifas-Shiman, S. L., Villamor, E., & Oken, E. (2013). Choline intake during pregnancy and child cognition at age 7 years. *American Journal of Epidemiology, 177,* 1338–1347.

Cheatham, C. L., Goldman, B. D., Fischer, L. M., da Costa, K. A., Reznick, J. S., & Zeisel, S. H. (2012). Phosphatidylcholine supplementation in pregnant women consuming moderate choline diets does not enhance infant cognitive function: A randomized, double-blind, placebo-controlled trial. *The American Journal of Clinical Nutrition, 96*(6), 1465–1472.

Cohen, E. L., & Wurtman, R. J. (1975). Brain acetylcholine: Increase after systematic choline administration. *Life Sciences, 16*(7), 1095–1102.

Cornford, E. M., Braun, L. D., & Oldendorf, W. H. (1978). Carrier mediated blood–brain barrier transport of choline and certain choline analogs. *Journal of Neurochemistry, 30*(2), 299–308.

Deuster, P. A. (2002). Choline ingestion does not modify physical or cognitive performance. *Military Medicine, 167*(12), 1020.

Eussen, S. J., Ueland, P. M., Clarke, R., Blom, H. J., Hoefnagels, W. H., Van Staveren, W. A., et al. (2007). The association of betaine, homocysteine and related metabolites with cognitive function in Dutch elderly people. *British Journal of Nutrition, 98*(05), 960–968.

Falleti, M. G., Maruff, P., Collie, A., & Darby, D. G. (2006). Practice effects associated with the repeated assessment of cognitive function using the CogState battery at 10-minute, one week and one month test-retest intervals. *Journal of Clinical and Experimental Neuropsychology, 28*(7), 1095–1112.

Hasselmo, M. E. (2006). The role of acetylcholine in learning and memory. *Current Opinion in Neurobiology, 16*(6), 710–715.

Haubrich, D. R., Wang, P. F., Clody, D. E., & Wedeking, P. W. (1975). Increase in rat brain acetylcholine induced by choline or deanol. *Life Science, 17,* 975–980.

Howe, J. C., Williams, J. R., Holden, J. M., Zeisel, S. H., & Mar, M. (2004). *USDA database for the choline content of common foods.* US Department of Agriculture, Agricultural Research Service, Beltsville Human Nutrition Research Center, Nutrient Data Laboratory.

Jiang, X., Yan, J., West, A. A., Perry, C. A., Malysheva, O. V., Devapatla, S., … Caudill, M. A. (2012). Maternal choline intake alters the epigenetic state of fetal cortisol-regulating genes in humans. *The FASEB Journal*, *26*(8), 3563–3574.

Jope, R. S. (1982). Effects of phosphatidylcholine administration to rats on choline in blood and choline and acetylcholine in brain. *Journal of Pharmacology and Experimental Therapeutics, 220,* 322–328.

Knott, V., de la Salle, S., Choueiry, J., Impey, D., Smith, D., Smith, M., et al. (2015a). Neurocognitive effects of acute choline supplementation in low, medium and high performer healthy volunteers. *Pharmacology Biochemistry and Behavior, 131,* 119–129.

Knott, V., de la Salle, S., Smith, D., Choueiry, J., Impey, D., Smith, M., … Labelle, A. (2015b). Effects of acute CDP-choline treatment on resting state brain oscillations in healthy volunteers. *Neuroscience Letters*, *591*, 121–125.

Ladd, S. L., Sommer, S. A., LaBerge, S., & Toscano, W. (1993). Brief report: Effect of phosphatidylcholine on explicit memory. *Clinical Neuropharmacology, 16*(6), 540–549.

Leermakers, E. T., Moreira, E. M., Kiefte-de Jong, J. C., Darweesh, S. K., Visser, T., Voortman, T., … Franco, O. H. (2015). Effects of choline on health across the life course: A systematic review. *Nutrition Reviews, 73*(8), 500–522.

Lockman, P., & Allen, D. (2002). The transport of choline. *Drug Development and Industrial Pharmacy, 28*(7), 749–771.

Naber, M., Hommel, B., & Colzato, L. S. (2015). Improved human visuomotor performance and pupil constriction after choline supplementation in a placebo-controlled double-blind study. *Scientific Reports, 5,* 13188.

Nag, N., & Berger-Sweeney, J. E. (2007). Postnatal dietary choline supplementation alters behavior in a mouse model of Rett syndrome. *Neurobiology of Disease, 26*(2), 473–480.

Nurk, E., Refsum, H., Bjelland, I., Drevon, C. A., Tell, G. S., Ueland, P. M., … Smith, D. A. (2013). Plasma free choline, betaine and cognitive performance: The Hordaland health study. *British Journal of Nutrition, 109*(03), 511–519.

Parnetti, L., Mignini, F., Tomassoni, D., Traini, E., & Amenta, F. (2007). Cholinergic precursors in the treatment of cognitive impairment of vascular origin: Ineffective approaches or need for re-evaluation? *Journal of the Neurological Sciences, 257*(1), 264–269.

Poly, C., Massaro, J. M., Seshadri, S., Wolf, P. A., Cho, E., Krall, E., … Au, R. (2011). The relation of dietary choline to cognitive performance and white-matter hyperintensity in the framingham offspring cohort. *The American Journal of Clinical Nutrition, 94*(6), 1584–1591.

Roth, G. S., Joseph, J. A., & Mason, R. P. (1995). Membrane alterations as causes of impaired signal transduction in Alzheimer's disease and aging. *Trends in Neurosciences, 18*(5), 203–206.

Rouser, G., & Yamamoto, A. (1968). Curvilinear regression course of human brain lipid composition changes with age. *Lipids, 3*(3), 284–287.

Signore, C., Ueland, P. M., Troendle, J., & Mills, J. L. (2008). Choline concentrations in human maternal and cord blood and intelligence at 5 y of age. *The American journal of clinical nutrition, 87*(4), 896–902.

Sitaram, N. (1978). Human serial learning: Enhancement with arecholine and choline and impairment with scopolamine. *Science, 201,* 1978.

Spiers, P. A., Myers, D., Hochanadel, G. S., Lieberman, H. R., & Wurtman, R. J. (1996). Citicoline improves verbal memory in aging. *Archives of Neurology, 53*(5), 441–448.

Trommer, B. A., Schmidt, D. E., & Wecker, L. (1982). Exogenous choline enhances the synthesis of acetylcholine only under conditions of increased cholinergic neuronal activity. *Journal of Neurochemistry, 39,* 1704–1709.

Ueland, P. M. (2011). Choline and betaine in health and disease. *Journal of Inherited Metabolic Disease, 34*(1), 3–15.

Williams, C. L., Meck, W. H., Heyer, D. D., & Loy, R. (1998). Hypertrophy of basal forebrain neurons and enhanced visuospatial memory in perinatally choline-supplemented rats. *Brain Research, 794*(2), 225–238.

Wu, D., & Hersh, L. B. (1994). Choline acetyltransferase: Celebrating its fiftieth year. *Journal of Neurochemistry, 62,* 1653–1663.

Yates, A. A., Schlicker, S. A., & Suitor, C. W. (1998). Dietary reference intakes: The new basis for recommendations for calcium and related nutrients, B vitamins, and choline. *Journal of the American Dietetic Association, 98*(6), 699–706.

Zeisel, S. H. (1981). Dietary choline: Biochemistry, physiology, and pharmacology. *Annual Review of Nutrition, 1*(1), 95–121.

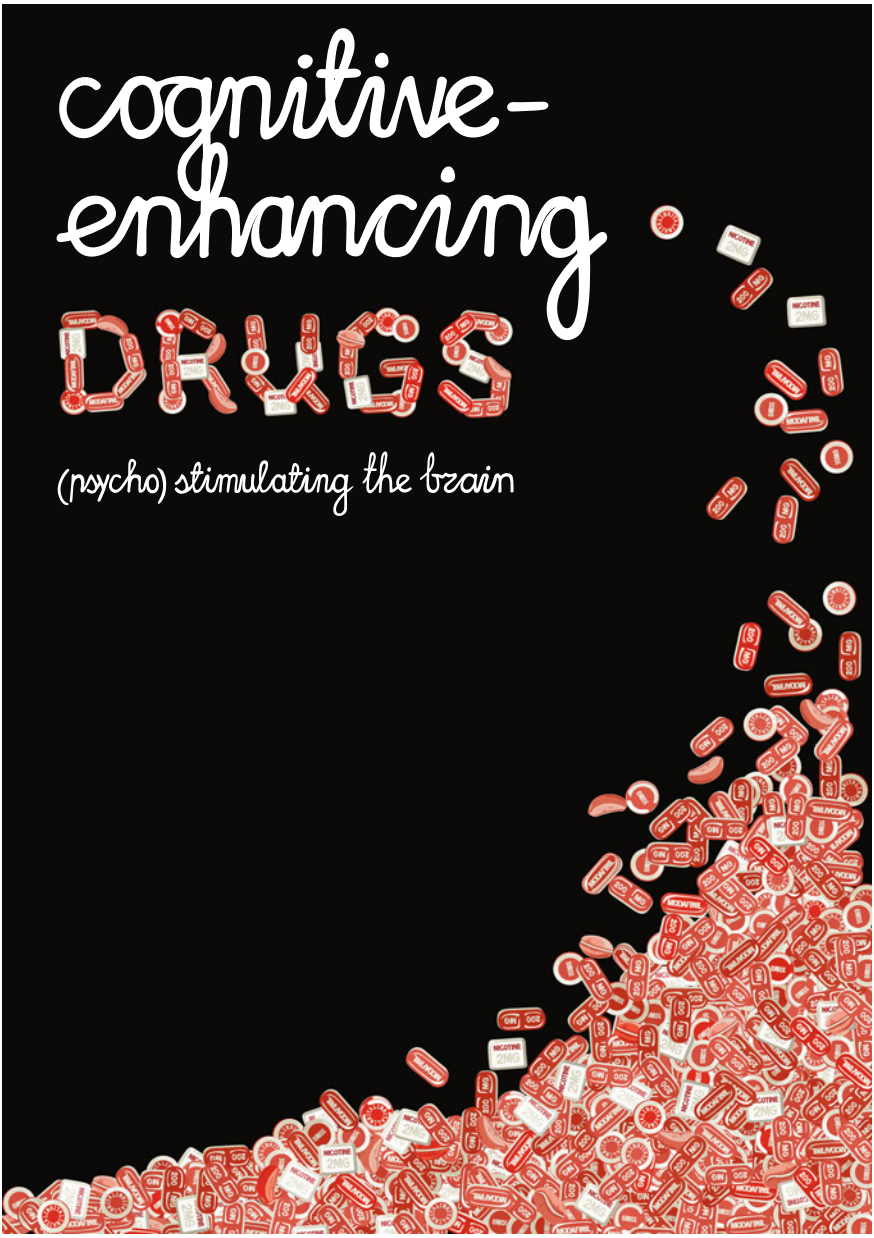
Zeisel, S. H., & Blusztajn, J. K. (1994). Choline and human nutrition. *Annual Review of Nutrition, 14*(1), 269–296.

Zeisel, S. H., Da Costa, K. A., Franklin, P. D., Alexander, E. A., Lamont, J. T., Sheard, N. F., et al. (1991). Choline, an essential nutrient for humans. *FASEB Journal: Official Publication of the Federation of American Societies for Experimental Biology, 5*(7), 2093–2098.

Zeisel, S. H., Mar, M. H., Howe, J. C., & Holden, J. M. (2003). Concentrations of choline-containing compounds and betaine in common foods. *The Journal of Nutrition, 133*(5), 1302–1307.

cognitive-enhancing DRUGS

(psycho) stimulating the brain



Part II
Cognitive-Enhancing Drugs—(Psycho)Stimulating the Brain

Introduction

The present part aims to explore the strategy to promote cognitive processes by means of psychostimulants, drugs that cause, at short- or long-term, improvements in mental functions. Cognitive-enhancing drugs can be divided in stimulants without prescription, such as caffeine and nicotine, and prescription medicines, such as Ritalin and Modafinil.

Caffeine and nicotine are the most widely consumed "legal" stimulants in the world. It has been estimated that in North America, 90% of adult population take caffeine daily. Besides an active ingredient of coffee, caffeine is contained in large amounts in energy drinks. Over the last few years the energy drink industry is flourishing, with sales of energy drinks estimated to be over 12.5 billion USD in 2012, an increase of 60% from 2008 to 2012 (Breda et al. 2014). Even though smoking decreased from 41.2% in 1980 to 31.1% in 2012, still in 2015, over 1.1 billion people in the world smoked tobacco (World Health Organization 2016). An interesting new trend in nicotine delivery, especially among young consumers aged 18–24, seems to rely on e-cigarettes. Indeed, in 2014, 12.6% of adults in the United States had ever tried an e-cigarette (Schoenborn and Gindi 2015).

Ritalin and Modafinil are the most consumed prescription medicines used to allegedly enhance mental performance (Sahakian and Morein-Zamir 2007). Although originally used for the treatment of attention deficit/hyperactivity disorder and narcolepsy, Ritalin and Modafinil have become the focus of scientific interest for their cognitive enhancing properties in healthy humans. Not surprisingly, these drugs are also called study drugs because they are used by students with the purpose of increase their academic performance. Because of this phenomenon the pharmacy industry is booming: in 2015 the company Novartis reported sales of Ritalin for over 365 million USD.

This part is devoted to clarify to what extent cognitive-enhancing drugs are really promoting cognitive functions. In the first part, stimulants without prescription, such as caffeine and nicotine, will be considered. Through their effect on the cholinergic system, the evidence about the consumption of caffeine (Chapter "Caffeine") and nicotine (Chapter "Nicotine") on cognition will be discussed. In the second part, prescription medicines, such as Ritalin and Modafinil, will be examined. By means of their effect on the dopaminergic and noradrenergic system, the effect of Ritalin (Chapter "Ritalin") and Modafinil (Chapter "Modafinil") on cognition will be illustrated.

References

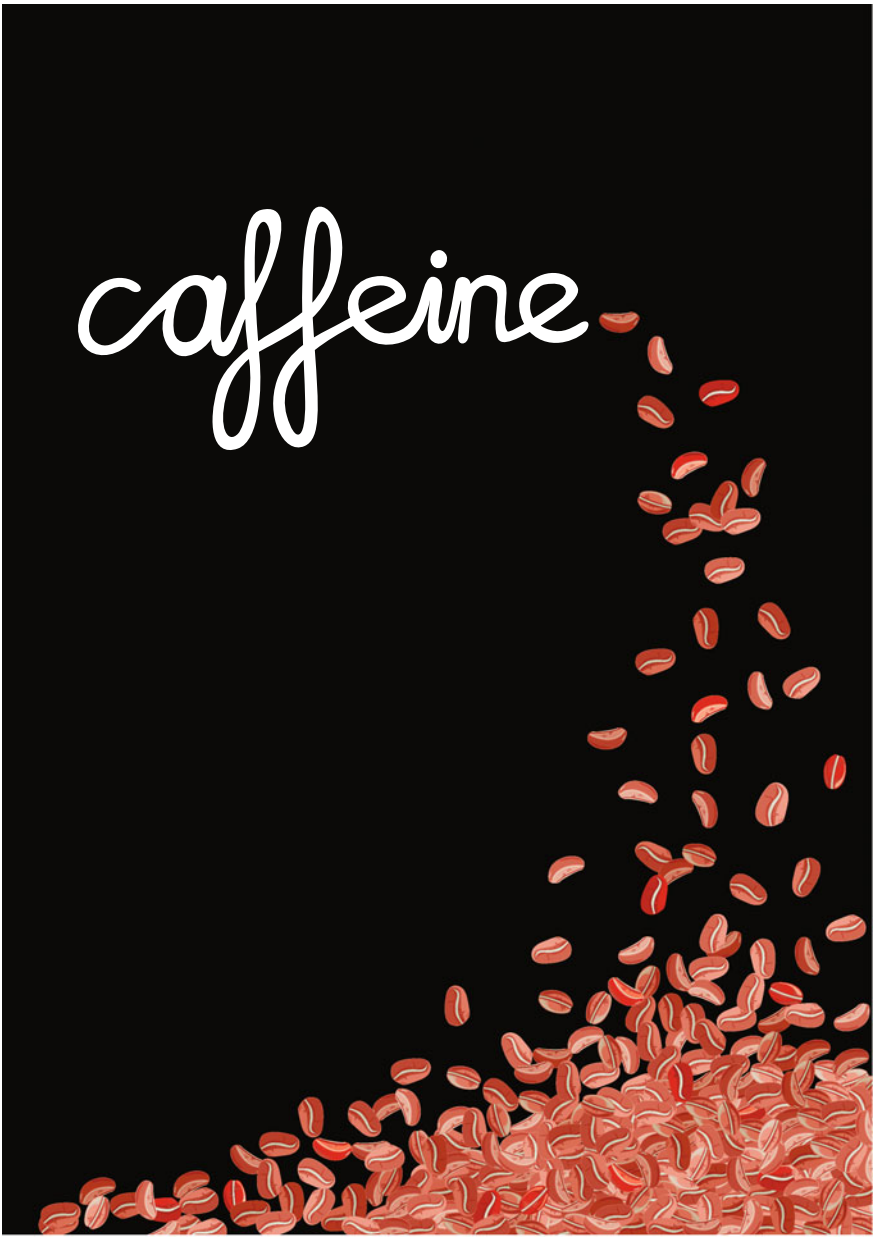
Breda, J. J., Whiting, S. H., Encarnação, R., Norberg, S., Jones, R., Reinap, M., & Jewell, J. (2014). Energy drink consumption in Europe: A review of the risks, adverse health effects, and policy options to respond. *Frontiers in Public Health, 2*, 134.

Novartis (2015). *Ritalin LA® product sales*. Retrieved from: https://www.novartis.com/investors/financial-data/product-sales

Sahakian, B., & Morein-Zamir, S. (2007). Professor's little helper. *Nature, 450*(7173), 1157–1159.

Schoenborn, C. A., & Gindi, R. M. (2015). Electronic cigarette use among adults: United States, 2014. *NCHS data brief, 217*, 1–8.

World Health Organization. (2016). *World Health Statistics 2016*. Retrieved from http://www.who.int/gho/publications/world_health_statistics/2016/en/


caffeine

Caffeine

Pauline van der Wel, Olga D. Boer and Lorenza S. Colzato

Introduction

Caffeine (1,3,7-trimethylxanthine) is a plant alkaloid that acts as a competitive antagonist of adenosine, thereby increasing the excitability of the sympathetic nervous system (SNS, Biaggioni et al. 1991). The psychostimulant effects of caffeine have been known for centuries and include increased levels of resting energy, enhanced physical and motor performance, increased alertness and wakefulness, and improved mood (for a review see Glade 2010). Given that caffeine has these stimulant properties, a lot of studies investigated the short- and long-term effectiveness of caffeine as cognitive enhancer (for reviews see Cappelletti et al. 2015; Panza et al. 2015). Unfortunately, reports on the effects of caffeine on cognitive performance in healthy humans are inconsistent and there is much variety in methodology and design (James 2014). A major issue that has been the topic of debate for many years is the hypothesis that caffeine derives its stimulant properties by reversal of withdrawal symptoms (James 1994, 2005). This hypothesis is supported by some studies (Ullrich et al. 2015), but rejected by others (Childs and De Wit 2006). The aim of this chapter is to provide a summary of available studies on the short- and long-term effects of caffeine on cognition in regular and nonusers in order to better understand under which circumstances caffeine has the potential to act as a cognitive enhancer.

P. van der Wel · O.D. Boer · L.S. Colzato (✉)
Cognitive Psychology Unit and Leiden Institute for Brain and Cognition,
Leiden University, Leiden, The Netherlands
e-mail: colzato@fsw.leidenuniv.nl

L.S. Colzato
Faculty of Psychology, Institute of Cognitive Neuroscience,
Ruhr University Bochum, Bochum, Germany

L.S. Colzato, *Theory-Driven Approaches to Cognitive Enhancement*,
DOI 10.1007/978-3-319-57505-6_4

In this chapter we will first describe the working mechanisms of caffeine and current issues in the debate on its effectiveness. Second, we will outline the available studies that investigate short- and long-term effects of caffeine on cognition. Studies on the short-term effects indicate that caffeine has the potential to enhance cognition in both regular and nonusers. Studies on the long-term effects indicate that long-term moderate caffeine consumption potentially decreases the risk of cognitive decline and dementia later in life.

Mechanism of Action

Approximately 45 min after oral ingestion, 99% of the administered dose of caffeine is absorbed from the gastrointestinal tract after which it immediately crosses the blood–brain barrier (Fredholm et al. 1999). Peak plasma levels are reached between 15 and 120 min and half-life values range from 1.5 to 9.5 h (Bonati et al. 1982). The length of these periods depends on individual absorption and metabolism rate, which are influenced by factors like age (Jarvis 1993) and smoking (Hart et al. 1976). Caffeine metabolism takes place in the liver and is mainly controlled by cytochrome CYP1A2 and to a lesser extent by xanthine oxidase and *N*-acetyltransferase (NAT2) (Fenster et al. 1998). Demethylation by these enzymes results in the release of three active metabolites: paraxanthine (84%), theobromine (12%), and theophylline (4%) (Bonati et al. 1982; Cappelletti et al. 2015) (see Fig. 1).

Caffeine modulates the activity of the sympathetic nervous system by blocking the effects of the naturally occurring neuromodulator adenosine. Adenosine in the brain inhibits the release of excitatory transmitters in the synaptic cleft, such as acetylcholine, dopamine, norepinephrine, and serotonin (Snyder 1985). Caffeine blocks A_1 and A_{2a} receptors, causing an increased release of dopamine, norepinephrine, and glutamate (Smits et al. 1987; Cappelletti et al. 2015). The relationship between A_{2a} receptors and D_1 and D_2 receptors also becomes obvious in their localization, both in a high concentration in dopamine rich areas in the brain (Smits et al. 1987; Cappelletti et al. 2015). When caffeine is ingested in higher doses (>500 to 600 mg), which is not likely to happen from dietary sources, other suggested mechanisms of action are mobilization of intracellular calcium and inhibition of phosphodiesterases (for a review see Cappelletti et al. 2015).

The European Food Safety Authority (2015) recommends a maximum caffeine intake of 400 mg/day with single doses not exceeding 200 mg. A regular cup of coffee is assumed to contain approximately 85–100 mg caffeine. The highest total caffeine concentrations (mg/100 g) are contained in 70–85% cacao dark chocolate (80 mg), coffee (40 mg), energy drink (30 mg), and tea (20 mg) (Somogyi 2010). At high single doses (e.g., >500 to 600 mg) caffeine can cause anxiety, tremor, and increased resting heart rate. Long-term health risks of high coffee consumption are cardiovascular diseases, negative shifts in calcium balance, and mineral

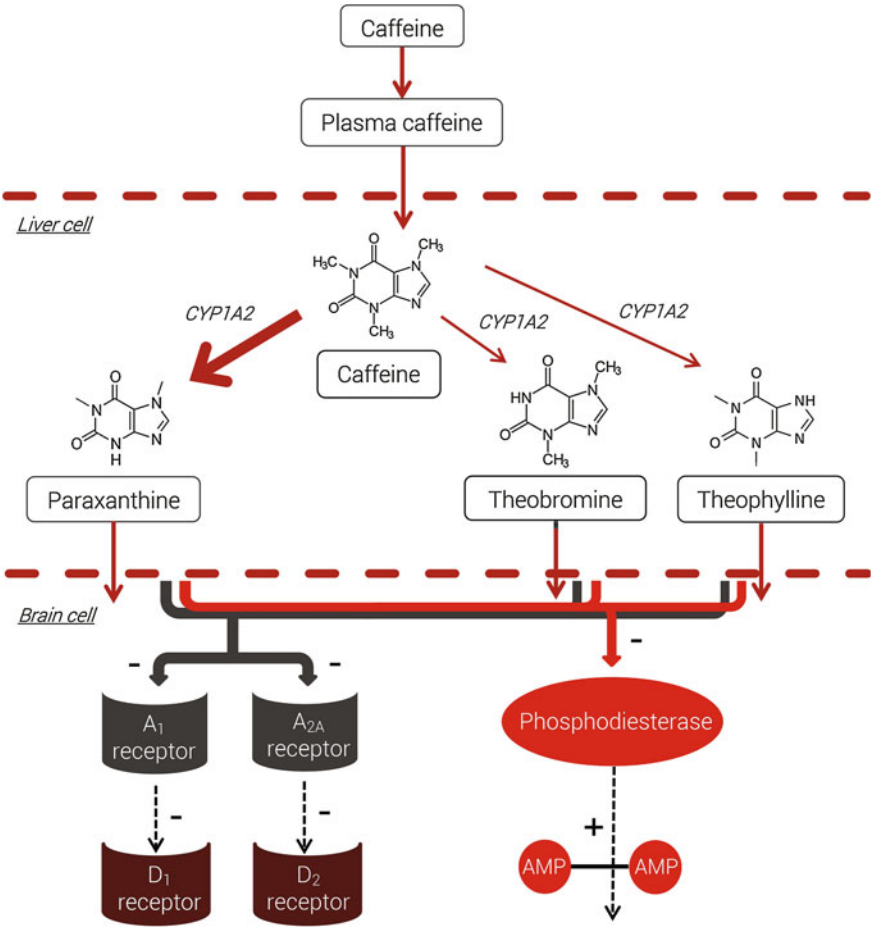


Fig. 1 Schematic representation of metabolism of caffeine and its mechanism of action. Caffeine is metabolized by CYP1A2 to paraxanthine (84%), theobromine (12%) and theophylline (4%) in the liver. After passing the blood–brain barrier, these substances block adenosine A1 and A2A receptors, that usually decrease the affinity of dopamine receptors for agonists. The substances also inhibit the enzyme phosphodiesterase, that breaks bonds in adenosine monophosphate (AMP), leading to more cyclic AMP (cAMP). The combination of both processes leads to the stimulatory effects of caffeine

deficiencies. However, these risks are mainly the result of a dose that is difficult to reach from dietary sources (Higdon and Frei 2006). Moreover, all lethal cases of caffeine intoxication known are the consequence of caffeine intake by non-dietary sources like pills (Cappelletti et al. 2015).

Short-Term Effects of Caffeine

The psychostimulant effects of caffeine are suggested to be beneficial not only for mood and alertness, but also for cognitive performance. In this section we will give an overview of findings on the acute cognitive enhancing properties of caffeine. We will first give a summary of a debate that dominated research on the effects of caffeine for years: the withdrawal reversal hypothesis of caffeine.

James (1994, 2005) was the first to argue that the acute effects of caffeine are largely due to reversal of withdrawal symptoms. Withdrawal symptoms of caffeine include headache, fatigue, decreased energy and alertness, and depressed mood (Juliano and Griffiths 2004). The withdrawal reversal hypothesis states that there are no net benefits of caffeine consumption, but rather that caffeine consumption after overnight abstention brings regular users back to their performance and energy baseline (Rogers et al. 2003). Several studies indeed show that their performance and alertness is impaired after overnight abstention (Richardson et al. 1995; for a review see James and Rogers 2005), but others do not (Haskell et al. 2005), or find even higher cognitive performance (Smit and Rogers 2000). Methodological issues such as the definition of caffeine-naivety, the possible self-selection of people that are caffeine naïve, and individual differences in caffeine sensitivity could be the cause of these inconsistent results (James 2014). Because it is yet unclear whether cognitive enhancing effects of caffeine are due to withdrawal reversal, short-term effects of caffeine will be discussed separately for regular and nonusers respectively.

Effects in Regular Users

Studies show a large variety in their definition of regular users. In line with the categorization of Cappelletti et al. (2015), we define regular users as people that consume 200–400 mg of caffeine on a daily basis. The results of studies investigating the acute cognitive enhancing effects of caffeine in regular users are mixed. Rogers et al. (2013) did not find an acute benefit of a single dose of 100–150 mg caffeine on mental alertness or mental performance in medium-high consumers after overnight abstention. However, the group of medium-high consumers was indicated by consuming >40 mg/day, which corresponds to the low-users group indicated by Cappelletti et al. (2015). In contrast, a study by Haskell et al. (2005) did show increased performance on two accuracy tasks after administrating 75 or 150 mg caffeine to regular consumers. The discrepancy between these studies shows that administrating a dose that lacks an effect in low consumers can have an effect in moderate consumers, which may point to support for the withdrawal reversal hypothesis. However, the study by Haskell et al. (2005) did not find lower performance on these tasks before caffeine administration after overnight abstention, so there were no apparent withdrawal symptoms.

A study that investigated the effect of low doses revealed a dose as low as 12.5 mg significantly improved cognitive performance on a simple reaction task and a rapid visual interaction task. These effects were more apparent in high

caffeine consumers (>200 mg/day), as compared to low caffeine consumers (<100 mg/day). Only the highest dose (100 mg) significantly increased levels of energetic arousal, equally for both groups (Smit and Rogers 2000). This study nicely shows two findings that are more or less consistent in the literature: Caffeine seems to be more beneficial for performance on simple cognitive tasks, and improvements in alertness and mood are possible confounds. A recent study in which there were no differences in cognitive performance between participants that received caffeine, placebo, water, or no treatment, supports that mood and alertness are possible confounds: the only trend to significance was found in subjective reports of preserved mental energy and activation after caffeine intake. Moreover, 24-h of caffeine abstinence did not result in an effect of caffeine or coffee placebo on cognitive performance (Ullrich et al. 2015).

From the Ullrich et al. (2015) and Smit and Rogers (2000) study we can conclude that the effect, or lack of effect, of caffeine on cognitive performance in regular users seems to be influenced by changes in mood. Besides mood, also the level of expectancy (Richardson et al. 1995) and baseline levels of arousal or alertness (Chait 1992) are suggested to have an influence on the effect of caffeine on cognitive performance. Since regular users are always aware of their overnight caffeine abstention, it is difficult to determine whether improved performance is a consequence of changes in expectancy, alertness, and mood, reversal of withdrawal symptoms, or the caffeine. Nonetheless, most studies hypothesize that the beneficial effect is largest when the baseline levels of alertness are low and expectancy of the effects of caffeine is high (Smith 2002).

A proper way to deal with the issues of caffeine research in regular users is to investigate if and how caffeine affects performance in nonusers. The results of these studies will be discussed in the next section.

Effects in Nonusers

Studies on caffeine supplementation to nonusers show significant subjective and objective effects in mood and performance. A study (Childs and de Wit 2006) showed that caffeine administration to nondependent, light users significantly increased blood pressure, feelings of arousal, positive mood reports, and measures of attention. However, an administration of the highest dose (450 mg) significantly impaired performance on a working memory task called the backward digit span task. Haskell et al. (2005) showed that in nonusers 150 mg of caffeine significantly improved performance on digit vigilance accuracy and reaction time, working memory reaction time, sentence verification accuracy (also after 75 mg), and delayed picture recognition time. Also, mental fatigue was significantly reduced after a dose of 75 mg. Thus, although more studies on the acute effects of caffeine in nonusers are needed, preliminary results suggest that caffeine administration to nonusers affects their subjective and objective state, which raises serious doubts about the withdrawal reversal hypothesis.

In sum, administration of caffeine affects mood, alertness, and cognitive performance in both regular- and nonusers. The largest effect is found when the task is easy, baseline alertness is low, and expectancy is high. More research is needed on the effects of caffeine in nonusers and the potential mediating or moderating role of mood, alertness, and expectancy in regular users.

Long-Term Effects of Caffeine

In a recent review of 28 cross-sectional and longitudinal studies, it was concluded that moderate intake of caffeine has the potential to decrease the risk on cognitive decline and dementia or Alzheimer's disease (AD) later in life (Panza et al. 2015). A survey including 9003 British adults showed a dose-response trend to improved performance with higher levels of caffeine consumption in simple reaction time, and memory tasks (Jarvis 1993). These promising findings lead us to the following section to discuss studies investigating the protective effect of caffeine in cognitive decline and impairment, and in dementia and AD.

Late-life cognitive decline, also called mild cognitive impairment (MCI), is defined as a reduction in cognitive abilities, usually in the domain of memory, that is unexpected at the particular age and level of education (Petersen et al. 1999). A large population study among 4197 women and 2820 men showed that the psychostimulant properties of caffeine are associated with a reduction in cognitive decline, especially in women. No relation was found in men (Ritchie et al. 2007). Other review studies point in the same direction (Arab et al. 2013; Panza et al. 2015), except one study that lacks an association when the model is fully adjusted for age, intelligent quotient score, and social class. When controlled for age and gender only, a significant positive association between caffeine intake and global cognitive functions was found (Corley et al. 2010).

Thus, these studies suggest that there is an association between caffeine intake and reductions in cognitive decline, but that confounds may play a large part in this association and possibly could account for a lack of a dose-response trend in some studies. In the next section, we will discuss studies on the effects of caffeine on prevention of dementia and AD, after which we will address some possible confounds and proposed working mechanisms.

AD is a neurodegenerative disease that is characterized by a progressive impairment of cognitive functions like memory and learning (Canas et al. 2009). The amyloid hypothesis states that AD is caused by accumulation of amyloid β-peptide (Aβ) in the brain. This accumulation is suggested to be the consequence of an imbalance between Aβ production and Aβ clearance due to mutations in the APP gene. As a consequence of Aβ accumulation, neuronal homeostasis and other processes on the cellular level are dysregulated, eventually leading to cell death and widespread neuronal dysfunction (Hardy and Selkoe 2002). Control of potential risk factors is thought to be the most beneficial treatment by preventing the early symptoms of Aβ accumulation. Dietary factors, such as caffeine, are becoming

more and more promising as they are recently associated with the risk for developing Alzheimer's disease (Eskelinen and Kivipelto 2010). Several studies suggest that caffeine is associated with a significantly lower risk of AD even when accounting for variables such as medical disorders, drugs, and education (Eskelinen and Kivipelto 2010; Maia and De Mendonça 2002). Animal research suggests that caffeine protects against Aβ accumulation by blockade of adenosine A_{2a} receptors, which otherwise would cause a loss of nerve terminal markers, resulting in Aβ imbalance and, consequently, memory dysfunction (Canas et al. 2009). Other suggested mechanisms are more indirect, but are also thought to be beneficial for reduction of cognitive decline. These indirect mechanisms include, among others, late-life health benefits of caffeine like prevention of type 2 diabetes, Parkinson's disease, and colorectal cancer (Higdon and Frei 2006).

Thus, according to the current knowledge, caffeine on the long term acts as a protective rather than a restorative factor and is associated with reduced cognitive decline and a lower risk of AD. It has also become clear that in research on the association between caffeine intake and cognitive decline or AD, there are many possible confounding variables. Both caffeine consumption and cognitive decline are associated with a wide range of sociodemographic, lifestyle and clinical variables, such as gender, social class, and intelligence (Ritchie et al. 2014). Although some studies corrected for these confounds, others did not, which can lead to biased results. Furthermore, research on AD and dementia are often of a retrospective nature and participants are usually of a high age. These factors may increase the chance of biased and incorrect consumption reports, which should be taken into account when interpreting the results. (Arab et al. 2013).

We conclude that the long-term effects of caffeine on cognitive performance are very promising, but since possible confounds are not addressed in many of the studies, more research is needed on this topic before firm conclusions can be drawn.

Conclusion

As an adenosine receptor antagonist, caffeine has the potential to exert a psychostimulant effect. Although more research is needed to explain contradictory results, the literature suggests that on the short term, caffeine can positively influence cognitive performance, in particular when the task is easy, baseline alertness is low, and expectancy is high. This effect is more consistent in regular users than in nonusers, which is why more research into the acute effects of caffeine in nonusers is needed. Furthermore, future studies should take into account participants' mood, alertness, and expectancy levels, since these confounds seem to play a large role in modulating the cognitive enhancing effect of caffeine.

Besides the suggested beneficial short-term effects, studies on the effects of long-term use of caffeine show very promising findings. Although results are still inconsistent, caffeine might be beneficial for reducing cognitive decline and lowering the risk of AD. More research is needed into direct and indirect working

mechanisms and on possible confounds such as lifestyle factors and gender differences.

Future studies should take into consideration adding genetic information as a covariate in their analyses, in order to achieve a better understanding of the role that particular polymorphisms might play in the effects of caffeine. A recent study suggested that a part of the interindividual variability in effects of caffeine on performance can be explained by variability in genes, in particular genes that affect adenosine metabolism (Renda et al. 2015). Caffeine in interaction with genes has not yet received much attention in the literature, but available studies point to polymorphisms in the CYP1A2 enzyme, adenosine A_{2a} receptor, or dopamine receptors to account for interindividual differences in caffeine sensitivity and caffeine effects on performance on both the short- and long-term (Yang et al. 2010).

In sum, even though more research is necessary, we can conclude that caffeine is a promising tool for enhancing cognitive performance on the short-term in both regular and non-regular users and might exert neuroprotective effects across the life span.

References

Arab, L., Khan, F., & Lam, H. (2013). Epidemiologic evidence of a relationship between tea, coffee, or caffeine consumption and cognitive decline. *Advances in Nutrition, 4,* 115–122.

Biaggioni, I., Paul, S., Puckett, A., & Arzubiaga, C. (1991). Caffeine and theophylline as adenosine receptor antagonists in humans. *Journal of Pharmacological Experimental Therapy, 258,* 588–593.

Bonati, M., Latini, R., Galletti, F., Young, J. F., Tognoni, G., & Garattini, S. (1982). Caffeine disposition after oral doses. *Clinical Pharmacology and Therapeutics, 32*(1), 98–106.

Canas, P. M., Porciúncula, L. O., Cunha, G. M. A., Silva, C. G., Machado, N. J., Oliveira, J. M. A., et al. (2009). Adenosine A_{2a} receptor blockade prevents synaptotoxicity and memory dysfunction caused by β-amyloid peptides via p38 mitogen-activated protein kinase pathway. *Journal of Neuroscience, 29,* 14741–14751.

Cappelletti, S., Daria, P., Sani, G., & Aromatario, M. (2015). Caffeine: Cognitive and physical performance enhancer or psychoactive drug? *Current Neuropharmacology, 13*(1), 71–88.

Chait, L. D. (1992). Factors influencing the subjective response to caffeine. *Behavioral Pharmacology, 3,* 219–228.

Childs, E., & De Wit, H. (2006). Subjective, behavioral and physiological effects of acute caffeine in light, nondependent caffeine users. *Psychopharmacology (Berl), 185,* 514–523.

Corley, J., Jia, X., Kyle, J. A. M., Gow, A. J., Brett, C. E., Starr, J. M., et al. (2010). Caffeine consumption and cognitive function at age 70: The Lothian birth cohort 1936 study. *Psychosomatic Medicine, 72,* 206–214.

Eskelinen, M. H., & Kivipelto, M. (2010). Caffeine as a protective factor in dementia and Alzheimer's disease. *Journal of Alzheimer's Disease, 20,* S167–S174.

European Food Safety Authority. (2015). Panel on dietetic products, nutrition and allergies. Scientific opinion on the safety of caffeine. *EFSA Journal, 13,* 4102.

Fenster, L., Quale, C., Hiatt, R. A., Wilson, M., Windham, G. C., & Benowitz, N. L. (1998). Rate of caffeine metabolism and risk of spontaneous abortion. *American Journal of Epidemiology, 147,* 503–510.

Fredholm, B. B., Bättig, K., Holmén, J., Nehlig, A., & Zvartau, E. E. (1999). Actions of caffeine in the brain with special reference to factors that contribute to its widespread use. *Pharmacological Reviews, 51*(1), 83–133.

Glade, M. J. (2010). Caffeine—not just a stimulant. *Nutrition, 26,* 932–938.

Hardy, J., & Selkoe, D. J. (2002). The amyloid hypothesis of Alzheimer's disease: Progress and problems on the road to therapeutics. *Science, 297,* 353–356.

Hart, P., Farrell, G. C., Cooksley, W. G., & Powell, L. W. (1976). Enhanced drug metabolism in cigarette smokers. *British Medical Journal, 2,* 147–149.

Haskell, C. F., Kennedy, D. O., Wesnes, K. A., & Scholey, A. B. (2005). Cognitive and mood improvements of caffeine in habitual consumers and habitual non-consumers of caffeine. *Psychopharmacology (Berl), 179*(4), 813–825.

Higdon, J. V., & Frei, B. (2006). Coffee and health: A review of recent human research. *Critical Reviews in Food Science and Nutrition, 46,* 101–123.

James, J. E. (1994). Does caffeine enhance or merely restore degraded psychomotor performance? *Neuropsychobiology, 30,* 124–125.

James, J. E. (2005). Caffeine-induced enhancement of cognitive performance: Confounding due to reversal of withdrawal effects. *Australian Journal of Psychology, 57,* 197–200.

James, J. E. (2014). Caffeine and cognitive performance: Persistent methodological challenges in caffeine research. *Pharmacology, Biochemistry and Behavior, 124,* 117–122.

James, J. E., & Rogers, P. J. (2005). Effects of caffeine on performance and mood: Withdrawal reversal is the most plausible explanation. *Psychopharmacology (Berl), 182,* 1–8.

Jarvis, M. J. (1993). Does caffeine intake enhance absolute levels of cognitive performance? *Psychopharmacology (Berl), 110,* 45–52.

Juliano, L. M., & Griffiths, R. R. (2004). A critical review of caffeine withdrawal: Empirical validation of symptoms and signs, incidence, severity, and associated features. *Pharmacology, 176,* 1–29.

Maia, L., & De Mendonça, A. (2002). Does caffeine intake protect from Alzheimer's disease? *European Journal of Neurology, 9,* 377–382.

Panza, F., Solfrizzi, V., Barulli, M. R., Bonfiglio, C., Guerra, V., Osella, A., et al. (2015). Coffee, tea, and caffeine consumption and prevention of late-life cognitive decline and dementia: A systematic review. *Journal of Nutrition and Healthy Aging, 19,* 313–328.

Petersen, R. C., Smith, G. E., Waring, S. C., Ivnik, R. J., Tangalos, E. G., & Kokmen, E. (1999). Mild cognitive impairment: Clinical characterization and outcome. *Archives of Neurology, 56,* 303–308.

Renda, G., Committeri, G., Zimarino, M., Di Nicola, M., Tatasciore, A., Ruggieri, B., et al. (2015). Genetic determinants of cognitive responses to caffeine drinking identified from a double-blind, randomized, controlled trial. *European Neuropsychopharmacology, 25,* 798–807.

Richardson, N. J., Rogers, P. J., Elliman, N. A., & O'Dell, R. J. (1995). Mood and performance effects of caffeine in relation to acute and chronic caffeine deprivation. *Pharmacology, Biochemistry and Behavior, 52,* 313–320.

Ritchie, K., Ancelin, M. L., Amieva, H., Rouaud, O., & Carrière, I. (2014). The association between caffeine and cognitive decline: Examining alternative causal hypotheses. *International Psychogeriatrics, 26,* 581–590.

Ritchie, K., Carrière, I., De Menconça, A., Portet, F., Dartigues, J. F., Rouaud, O., et al. (2007). The neuroprotective effects of caffeine: A prospective population study. *Neurology, 69,* 536–545.

Rogers, P. J., Heatherley, S. V., Mullings, E. L., & Smith, J. E. (2013). Faster but not smarter: Effects of caffeine and caffeine withdrawal on alertness and performance. *Psychopharmacology (Berl), 226*(2), 229–240.

Rogers, P. J., Martin, J., Smith, C., Heatherley, S. V., & Smit, H. J. (2003). Absence of reinforcing, mood and psychomotor performance effects of caffeine in habitual non-consumers of caffeine. *Psychopharmacology (Berl), 167,* 54–62.

Smit, H. J., & Rogers, P. J. (2000). Effects of low doses of caffeine on cognitive performance, mood and thirst in low and higher caffeine consumers. *Psychopharmacology (Berl), 152*(2), 167–173.

Smith, A. (2002). Effects of caffeine on human behavior. *Food and Chemical Toxicology, 40,* 1243–1255.

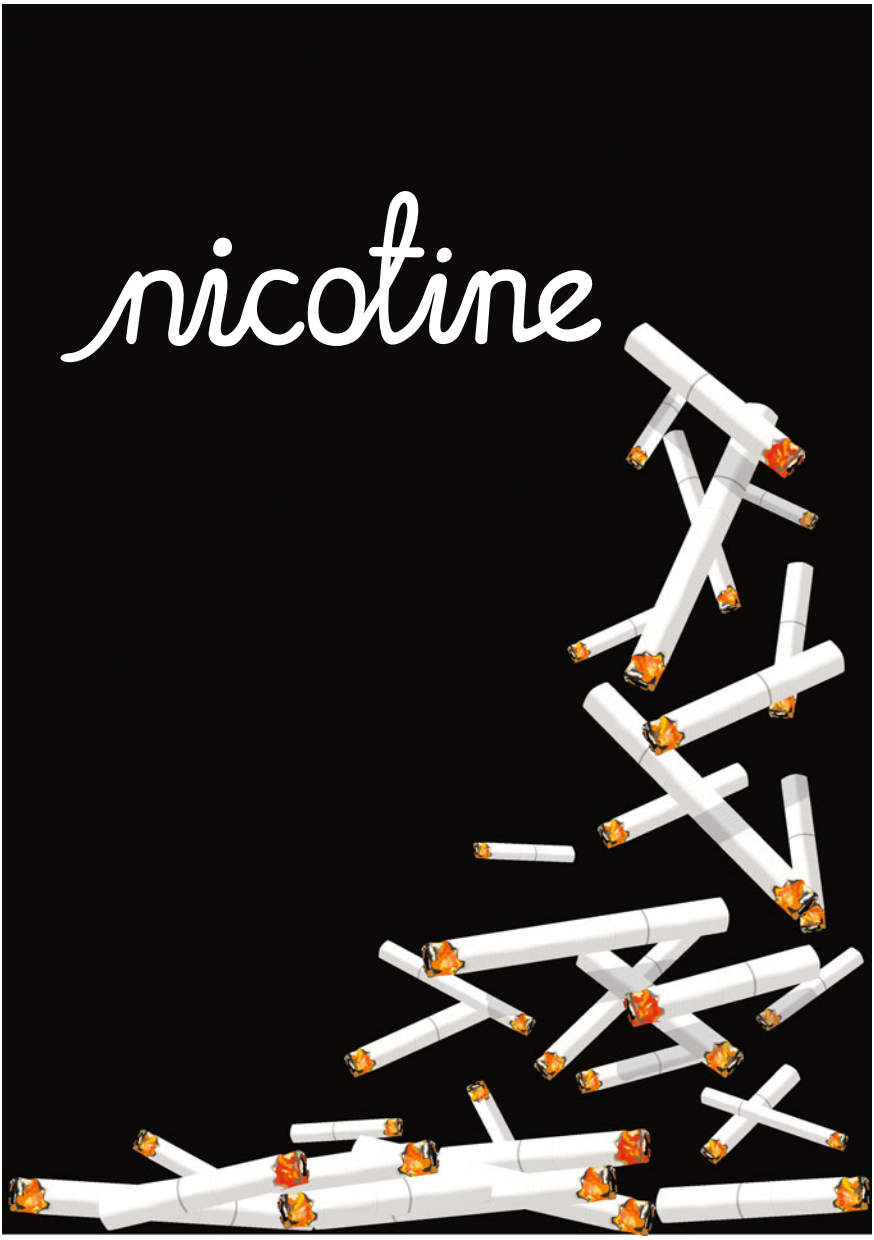
Smits, P., Boekema, P., De Abreu, R., Thien, T., & Van't Laar, A. (1987). Evidence for an antagonism between caffeine and adenosine in the human cardiovascular system. *Journal of Cardiovascular Pharmacology, 10,* 136–143.

Snyder, S. H. (1985). Adenosine as a neuromodulator. *Annual Review of Neuroscience, 8,* 103–124.

Somogyi, L. P. (2010). Caffeine Intake by the U.S. Population. http://www.fda.gov/downloads/aboutfda/centersoffices/officeoffoods/cfsan/cfsanfoiaelectronicreadingroom/ucm333191.pdf

Ullrich, S., De Vries, Y. C., Kühn, S., Repantis, D., Dresler, M., & Ohla, K. (2015). Feeling smart: Effects of caffeine and glucose on cognition, mood and self-judgment. *Physiology & Behavior, 151,* 629–637.

Yang, A., Palmer, A. A., & De Wit, H. (2010). Genetics of caffeine consumption and responses to caffeine. *Psychopharmacology (Berl), 211,* 245–257.


nicotine

Nicotine

Lorenza S. Colzato and Iris Spruit

Introduction

Nicotine is an alkaloid found in tobacco leaves that are processed and smoked. Nicotine is known for its addictive nature and, according to the World Health Organization, six million tobacco smokers die annually as a result of smoking (World Health Organization 2016). In 2015, over 1.1 billion people in the world smoked tobacco (World Health Organization 2016). Smoking occurs more in men than in women. Globally, smoking decreased from 41.2% in 1980 to 31.1% in 2012 in men and from 10.6 to 6.2% in women (Ng et al. 2014). In the United States 16.8% of the adults aged 18 years and older smoke cigarettes of which 18.8% is male and 14.8% is female (Jamal et al. 2015). Smoking is most prevalent in adults aged 25–44 years (20.0%) and least in adults over 65 years (8.5%). Furthermore, American Indians and Alaska Natives smoke the most (29.2%) and American Asians the least (9.5%). Also, smoking is more prevalent among individuals with a low education than high education and more prevalent among individuals that live below the poverty level (26.3%) than above the poverty level (15.2%; Jamal et al. 2015).

Recently a new phenomenon in nicotine delivery has come to light: electronic cigarettes (e-cigarettes). E-cigarettes are electronic delivery systems physically similar to cigarettes, but functionally different. Instead of burning tobacco leaves and producing tar, e-cigarettes aerosolize liquid nicotine from a disposable

L.S. Colzato (✉) · I. Spruit
Cognitive Psychology Unit and Leiden Institute for Brain and Cognition, Leiden University, Leiden, The Netherlands
e-mail: colzato@fsw.leidenuniv.nl

L.S. Colzato
Institute of Cognitive Neuroscience, Faculty of Psychology, Ruhr University Bochum, Bochum, Germany

L.S. Colzato, *Theory-Driven Approaches to Cognitive Enhancement*,
DOI 10.1007/978-3-319-57505-6_5

container. The absence of tar from the aerosol has two main advantages. First, many of the dangerous chemicals incorporated in tobacco cigarettes are supposedly absent. Second, the different composition of particulate matter implies that nicotine delivery is slowed, reducing the addiction potential. Accordingly, e-cigarettes have been considered a safe alternative to smoking. However, while the levels of perilous chemicals are indeed largely minimized in e-cigarettes, a recent review of 48 studies suggests there is no evidence for a decreased addiction potential (Grana et al. 2014). Therefore, e-cigarettes seem to be a helpful harm-reduction agent, but not a cure for nicotine addicts.

In the brain nicotine promotes the function of acetylcholine (ACh), because it binds on nicotinic acetylcholine receptors (nAChRs; Briley and Changeux 1977). The cholinergic system plays a major part in various cognitive functions, including learning, memory, and attention (Everitt and Robbins 1997). Nicotine administration increases nicotine blood plasma concentration and nicotine concentration in the brain. It binds on nAChRs and thereby facilitates the release of several neurotransmitters critical for cognitive functioning such as dopamine (dos Santos Coura and Granon 2012). The effects nicotine exerts on cognition has been studied extensively over the past few decades (for extensive reviews see Newhouse et al. 2004; Swan and Lessov-Schlagger 2007). Reports of the acute effect of nicotine are abundant, but inconsistent. The chronic (long-term) effects of nicotine have been less studied. The goal of chapter is to give an overview of the studies that investigated the effect of nicotine on cognition in healthy humans in order to get a better understanding under which conditions nicotine can enhance cognition and to elucidate whether nicotine can function as a cognitive enhancer.

In this chapter we will first explain how nicotine administration affects the cholinergic system. Then, we will review the studies that investigated the acute effects of nicotine. Finally, we will outline studies that examined the long-term effect of nicotine on cognition. The studies show that nicotine at short term can potentially enhance attentional and memory processes, but only in poor performers. Nicotine at long term can also enhance cognition, mainly attention, but only in the elderly with cognitive deficits.

Mechanism of Action

In the brain, nicotine binds to nicotinic acetylcholine receptors (nAChRs) that are ordinarily activated by the neurotransmitter acetylcholine (Briley and Changeux 1977; Poorthuis et al. 2009). Nicotine inhaled through smoking is rapidly absorbed into the lungs, which results in high concentrations of nicotine in the blood that leaves the heart and this blood reaches the brain within 8–10 s (Matta et al. 2007). Nicotine blood levels are highest after a cigarette is smoked and then drop quickly over the next 20 min. The elimination half-life of nicotine is about 2 h. There are several methods of nicotine administration for experimental purposes, but the ones most used in the literature seem to be transdermal exposure through nicotine

patches or nicotine gum. The nicotine patch Nicoderm results in peak levels of nicotine within 4 h of administration, while other patches result in peak levels after 6–9 h (Gore and Chien 1998). When chewing nicotine gum, nicotine levels rise increasingly over 15–30 min and, important to note, only about half of the nicotine in the gum is absorbed (Shiffman et al. 2002). After administration, nicotine is transported across the blood–brain barrier (see Fig. 1). In the brain, nicotine binds to nAChRs, which can be found widespread throughout the brain including the prefrontal cortex, thalamus, hippocampus, and monoamine-containing nuclei such as the substantia nigra, raphe nuclei, locus coeruleus, and ventral tegmental area. nAChRs consist of unique combinations from at least 12 subunits (α2–α10, β2–β4; Wu and Lukas 2011). The receptors are either heteromeric (e.g., α4β2) or homomeric (e.g., α7). The α4β2 receptor is the most common in the mammalian brain and because this receptor is highly sensitive to nicotine, it desensitizes at low concentrations of nicotine that correspond to blood concentrations in smokers (Millar and Gotti 2009; Wu et al. 2006). The saturation of nAChRs is dose-dependent. Smoking one cigarette (1.2–1.4 mg of nicotine) results in nearly complete occupation of α4β2 receptors (88%) 3.1 h after smoking and it is thought that smokers maintain an almost full α4β2 nAChR saturation (96–98%) throughout the day (Brody et al. 2006). Smoking only three puffs resulted in 75% of α4β2 occupancy 3.1 h after smoking (Brody et al. 2006).

Short-Term Effects of Nicotine

Although numerous studies investigated the acute effect of nicotine on cognition, the results are mixed. In this section, we will give an overview of the recent findings involving the acute effects of nicotine and explain which factors may cause the contradictory results.

Nicotine seems to enhance cognition in several domains, but mainly attention and memory. This was demonstrated by Heishman et al. (2010), who performed a meta-analysis on 41 studies published from 1994 to 2008. These studies all used a double-blind, placebo-controlled design and the participants consisted of healthy nonsmoking or smoking adults who were not or minimally deprived from tobacco (≤ 2 h). Studies with participants who were nicotine-deprived were excluded from the analysis due to the reversed-withdrawal effect. This means that when deprived smokers are administered nicotine, the enhanced cognitive performance is only due to the reversal of performance deficits caused by withdrawal. The authors found enhancing effects of nicotine limited to attention (alerting and orienting), and memory (episodic and working memory). Nevertheless, some studies published after this meta-analysis show no cognitive enhancing effects of nicotine. Grundey et al. (2015) assessed the effect of nicotine, in the form of a nicotine patch releasing 15 mg over 16 h, on working memory, which was measured with the n-back task, and attention, which was measured with the Stroop task in nonsmokers and nicotine-deprived smokers. Compared to nonsmokers, nicotine-abstinent smokers

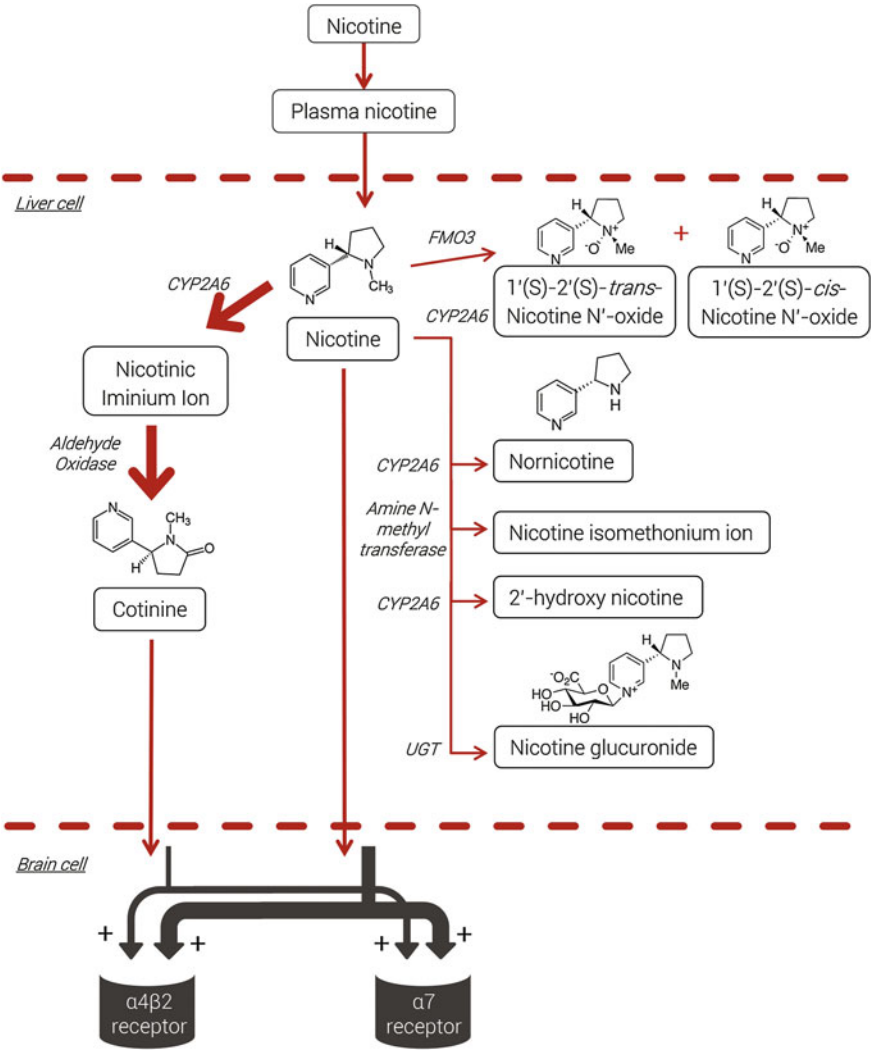


Fig. 1 Schematic representation of nicotine metabolism. When nicotine enters the liver through circulation it is metabolized into 6 primary metabolites, primarily cotinine (70–80%) through the intermediary metabolite nicotinic iminium ion. Nicotine not metabolized crosses the blood–brain barrier and binds agonistically to nicotinic acetylcholine receptors (nAChR's) in the brain. Cotinine also binds to nAChR's agonistically but with lower affinity than nicotine. The α4β2 and α7 receptors shown here represent 90% of nAChR's in the mammalian central nervous system, but 13 other types are known. Metabolism in the liver occurs mostly through the enzyme cytochrome P450 2A6 (CYP2A6). Other enzymes include Flavin-containing monooxygenase 3 (FMO3), uridine diphosphate-glucuronosyltransferase (UGT), amine *N*-methyltransferase and aldehyde oxidase

showed deficit in working memory and attentional control. However, the intake of nicotine improved performance of both cognitive processes in smokers, but performance worsened in nonsmokers. This effect was especially clear for working memory performance. However, these findings are not in line with findings of another study. Fisher et al. (2012) found that nicotine did not improve working memory. In this placebo-controlled study, nonsmoking healthy adults received 6 mg of nicotine gum. Nicotine did not affect response speed or accuracy on the n-back task, which, using different loads, measures the ability to update and monitor task-relevant information in working memory. The contradictory results of these two studies may be explained by the different doses of nicotine employed. Indeed, in order to get some nicotine-facilitated neurotransmitter responses, a sufficient level of nicotine is necessary (Balfour 2004).

Even though an adequate dose of nicotine is crucial to get a beneficial effect, high nicotine doses can have an adverse effect on cognition. Poltavski et al. (2012) investigated the effect of different doses, administered through nicotine patches (7, 14, and 21 mg), on cognitive performance and found an inverted u-shaped relationship between different doses of nicotine and cognitive performance. Indeed, as previously pointed out by Newhouse et al. (2004), moderate nicotine intake can produce optimal performance, whereas low or high nicotine intake can impair performance. The idea is that only suboptimal performing individuals can benefit from nicotine administration. However, if individuals are already performing optimally, nicotine administration will impair performance as in the case of the nonsmokers in the study by Grundey et al. (2015) previously discussed. This idea is supported by studies showing the nicotine can act as cognitive enhancer in low-performing clinical populations such as Alzheimer's disease, schizophrenia or attention deficit hyperactivity disorder (ADHD) (see Newhouse et al. 2004 for a review). In a seminal study Potter and Newhouse (2008) investigated how acute nicotine administration, in the form of a nicotine patch (7 mg, administered for 45 min), affects several cognitive functions in 15 nonsmoking young adults diagnosed with ADHD. After nicotine administration, the participants showed improvement in behavioral inhibition and a tendency, even if not significant, of improvement in recognition memory.

Another factor that contributes to mixed results in the literature may be the genetic predisposition. Indeed, Ahrens and colleagues (2015) showed that the individual variability in the effects of nicotine on cognition could be explained by variation in dopaminergic (DRD2) and cholinergic (CHRNA4) genes. In this study, employing a within-subject, double-blind, placebo-controlled crossover design, nicotine was administered to healthy nonsmoking adults in the form of a nicotine patch (7 mg, administered for 1 h). The participants performed a visual search task with different load conditions and distractors. The results pointed to the conclusion that the effects of nicotine on distractor interference are moderated jointly by cholinergic and dopaminergic genetic variations (Ahrens et al. 2015).

In conclusion, acute nicotine administration promotes cognition but this effect seems to be limited to the domains of attention and memory. Further, this effect seems to differ depending on the dose of nicotine, the genetic predisposition, and the individual baseline performance level. At short term, nicotine acts as a cognitive enhancer in low-performing, but not in already optimally performing individuals.

Long-Term Effects of Nicotine Across the Life Span

In this section we will outline studies that investigated the chronic effects of nicotine across the life span. Several animal studies suggest that prenatal exposure to nicotine has adverse effects on cognitive functioning. For instance, the offspring of rat dams that were injected with 2 mg/kg of nicotine a day showed memory deficits compared to a control group (Levin et al. 1996). The effect of prenatal nicotine exposure on cognition in humans is less clear. In one study, 10-year old children (n = 593), of which little over half was prenatally exposed to smoking, were assessed on measures of learning, memory, and problem solving. After controlling for several maternal characteristics, such as other prenatal substance use and sociodemographic variables, the authors found that prenatal exposure to smoking was related to impairments in learning and memory (Cornelius et al. 2001). On the other hand, another study could not replicate this outcome. Kafouri et al. (2009) investigated the association between prenatal exposure to cigarettes and cognition in 503 adolescents, aged 12–18 years. Nicotine-exposed participants were matched with nonexposed participants by education of the mother and school attended. Several cognitive functions were measured, including visuospatial skills, verbal and visual memory, processing speed and inhibition. No effect of prenatal cigarette exposure on cognitive abilities was found. As suggested by Clifford et al. (2012) in their review, the reductions in cognitive performance due to prenatal nicotine exposure are generally small and can sometimes at least in part be attenuated by maternal characteristics, such as IQ, education, and other factors.

Given that many smokers started smoking during adolescence, several researchers have focused their interest in investigating the chronic effect of smoking on cognitive functioning during adolescence. One study found that adolescent smokers, aged 14–18 years, showed poorer performance in working memory and divided attention than nonsmokers, while both groups were comparable in age, gender, and education (Jacobsen et al. 2005). Furthermore, they found that performance was worse in smokers that started smoking on an earlier age, than in smokers that started on a later age. These findings concur with another study in which it was found that smokers who started smoking during adolescence performed worse on a working memory task (as indexed by the n-back task) than nonsmokers (Ernst et al. 2001). No difference was found between smokers and nonsmokers in visual attention or logical reasoning. Another study examined the prefrontal attentional network function using functional magnetic resonance imaging in smokers and nonsmokers (aged 18–25 years) while they performed an oddball task (Musso et al. 2007). Although they found no difference in reaction time between smokers and nonsmokers, activity in the prefrontal attentional network was lower in smokers than in nonsmokers. Moreover, smoking duration was associated with the degree of reduced attentional network activity. Note that these studies did not assess the effect of nicotine alone. Cigarette smoke (both mainstream and sidestream) consists of various other substances, such as tar, that could possibly influence the brain (Fowles and Dybing 2003). Furthermore, although the

previously mentioned studies controlled for several possibly confounding variables like age, gender, and education, it is still possible that other variables such as social environment and genetic variability might have impacted the results. Nevertheless, it has been suggested that during adolescence nicotine can induce changes in gene expression and neuronal morphology in the prefrontal cortex, which not surprisingly, could explain the negative repercussion on cognition in adulthood (Poorthuis et al. 2009). Further evidence that exposure to nicotine during adolescence may have long-lasting effects on cognition comes from a study with rats (Counotte et al. 2009). In this study, male rats were infused with either nicotine (0.4 mg/kg three times daily) or saline for 10 days during adolescence. Attentional performance was assessed 5 weeks after the last injection. Rats that received nicotine during adolescence showed reduced attentional performance, while rats that received nicotine during adulthood showed normal attentional performance.

Although nicotine exposure during adolescence seems to have a negative effect on cognition, long-term nicotine exposure can ameliorate cognitive deterioration in the elderly population. Nicotine seems to have a positive effect on attention in individuals with Alzheimer's disease. In a double-blind, placebo controlled, crossover study, 8 participants with Alzheimer's disease (mean age = 77) wore a nicotine patch for 4 weeks with doses of 5 mg/day during week 1 and 4, and 10 mg/day during week 2 and 3 (White and Levin 1999). Nicotine significantly enhanced attentional performance, which was assessed with Conners continuous performance test (CPT), whereas there was no significant effect on motor or memory performance. Nicotine also seems to have a positive effect on cognition in the mildly cognitive impaired elderly population. In a double-blind clinical study, 67 nonsmoking participants (age > 55) with mild cognitive impairments received either a nicotine patch (15 mg a day) or placebo patch for 6 months (Newhouse et al. 2012). Attentional performance and several other cognitive functions were assessed using the CPT and the cognitive drug research computerized battery. Nicotine treatment improved performance in attention, memory, and mental processing tasks. White and Levin (2004) also found an improvement in attention and memory due to long-term nicotine exposure. In their double-blind, placebo-controlled, crossover study, 11 nonsmoking participants with age-associated memory impairment (mean age = 75) wore nicotine patches during a 4-week period with the following doses: 5 mg/day during week 1 and 4, and 10 mg/day during week 2 and 3. Outcomes of the clinical global impression scale showed a significant improvement in memory symptoms when participants were treated with nicotine compared to placebo. Also attention performance improved as measured by the CPT.

In sum, long-term nicotine exposure seems to have different effects across the life span. Prenatal nicotine exposure possibly impairs cognition in later life and adolescent exposure to nicotine seems to negatively affect memory and attention in adulthood. Nicotine exposure later in life, however, shows promising effects on attention and possibly memory.

Conclusion

As it binds to nAChRs, nicotine has the potential to influence primarily the cholinergic system and secondarily other neurotransmitters critically relevant for cognitive functioning such as dopamine. Even though more research is necessary to further elucidate the effect of nicotine on cognition, at short- term, nicotine seems to improve mainly memory and attention and this effect seems to be restricted to low-performing individuals. This might be due to an inverted u-shaped relationship between nicotine and cognitive performance. Therefore, future studies that investigate the cognitive enhancing effects of nicotine should consider individual variations in performance.

Long-term nicotine exposure has different effects across the life time. Prenatal nicotine exposure seems to have slight adverse effects on cognition, although more research is necessary to disentangle the effects of nicotine from factors like social environment and genetics. In adolescence, nicotine exposure seems to also exert adverse effects on cognition and this might be due to changes in gene expression and neural morphology in the prefrontal cortex. Only in elderly population nicotine has the potential to enhance cognition, specifically attention. Accordingly, nicotine may be a promising tool for cognitive enhancement in restoring cognitive decline in aging.

Future studies should further investigate the neurological basis underlying the cognitive enhancing effect of nicotine. As studies have shown that genetic variability may have a modulatory effects on the nicotine-induced effects (Ahrens et al. 2015), genetic variability should be taken into account. Future studies could investigate whether individuals with genetic variability associated with suboptimal level of acetylcholine and dopamine will indeed benefit from nicotine administration.

In sum, although more research is needed and keeping in mind that six million tobacco smokers die annually as a result of smoking, we conclude that nicotine may have the potential to enhance attention and memory in low-performing individuals and individuals showing cognitive decline. Especially for the elderly and cognitively impaired population nicotine might offer cognitive benefits.

References

Ahrens, S., Markett, S., Breckel, T. P. K., Behler, O., Reuter, M., & Thiel, C. M. (2015). Modulation of nicotine effects on selective attention by DRD2 and CHRNA4 gene polymorphisms. *Psychopharmacology (Berl), 232,* 2323–2331.

Balfour, D. J. (2004). The neurobiology of tobacco dependence: A preclinical perspective on the role of dopamine projections to the nucleus accumbens. *Nicotine & Tobacco Research, 6,* 899–912.

Briley, M. S., & Changeux, J. P. (1977). Isolation and purification of the nicotinic acetylcholine receptor and its functional reconstitution into a membrane environment. *International Review of Neurobiology, 20,* 31–63.

Brody, A. L., Mandelkern, M. A., London, E. D., Olmstead, R. E., Farahi, J., Scheibal, D., … Mukhin. (2006). Cigarette smoking saturates brain α4β2 nicotinic acetylcholine receptors. *Archives of General Psychiatry, 63,* 907–914.

Clifford, A., Lang, L., & Chen, R. (2012). Effects of maternal cigarette smoking during pregnancy on cognitive parameters of children and young adults: A literature review. *Neurotoxicology and Teratology, 34,* 560–570.

Cornelius, M., Ryan, C., Day, N., Goldschmidt, L., & Willford, J. (2001). Prenatal tobacco effects on neuropsychological outcomes among preadolescents. *Journal of Developmental and Behavioral Pediatrics, 22,* 217–225.

Counotte, D. S., Spijker, S., van der Burgwal, L. H., Hogenboom, F., Schoffelmeer, A. N. M., de Vries, R. J., et al. (2009). Long-lasting cognitive deficits resulting from adolescent nicotine exposure in rats. *Neuropsychopharmacology, 34,* 299–306.

Dos Santos Coura, R., & Granon, S. (2012). Prefrontal neuromodulation by nicotinic receptors for cognitive processes. *Psychopharmacology (Berl), 221,* 1–18.

Ernst, M., Heishman, S. J., Spurgeon, L., & London, E. D. (2001). Smoking history and nicotine effects on cognitive performance. *Neuropsychopharmacology, 25,* 313–319.

Everitt, B. J., & Robbins, T. W. (1997). Central cholinergic systems and cognition. *Annual Review of Psychology, 48,* 649–684.

Fisher, D. J., Daniels, R., Jaworska, N., Knobelsdorf, A., & Knott, V. J. (2012). Effects of acute nicotine administration on behavioral and neural (EEG) correlates of working memory in non-smokers. *Brain Research, 1429,* 72–81.

Fowles, J., & Dybing, E. (2003). Application of toxicological risk assessment principle to the chemical constituents of cigarette smoke. *Tobacco Control, 12,* 424–430.

Gore, A. V., & Chien, Y. W. (1998). The nicotine transdermal system. *Clinical Dermatology, 16,* 599–615.

Grana, R., Benowitz, N., & Glantz, S. A. (2014). E-cigarettes: A scientific review. *Circulation, 129*(19), 1972–1986.

Grundey, J., Amu, R., Ambrus, G. G., Batsikadze, G., Paulus, W., & Nitsche, M. A. (2015). Double dissociation of working memory and attentional processes in smokers and non-smokers with and without nicotine. *Psychopharmacology (Berl), 232,* 2491–2501.

Heishman, S. J., Kleykamp, B. A., & Singleton, E. G. (2010). Meta-analysis of the acute effects of nicotine and smoking on human performance. *Psychopharmacology (Berl), 210,* 453–469.

Jacobsen, L. K., Krystal, J. H., Mencl, W. E., Westerveld, M., Frost, S. J., & Pugh, K. R. (2005). Effects of smoking and smoking abstinence on cognition in adolescent tobacco smokers. *Biological Psychiatry, 57,* 56–66.

Jamal, A., Homa, D. M., O'Connor, E., Babb, E., Caraballo, R. S., Singh, T., et al. (2015). Current cigarette smoking among adults—United states, 2005–2014. *Morbidity and Mortality Weekly Report, 64,* 1233.

Kafouri, S., Leonard, G., Perron, M., Richer, L., Seguin, J. R., Veillette, S., et al. (2009). Maternal cigarette smoking during pregnancy and cognitive performance in adolescence. *International Journal of Epidemiology, 38,* 158–172.

Levin, E. D., Wilkerson, A., Jones, J. P., Christopher, N. C., & Briggs, S. J. (1996). Prenatal nicotine effects on memory in rats: Pharmacological and behavioral challenges. *Developmental Brain Research, 97,* 207–215.

Matta, S. G., Balfour, D. J., Benowitz, N. L., Boyd, R. T., Buccafusco, J. J., Caggiula, A., … Zirger, J. M. (2007). Guidelines on nicotine dose selection for in vivo research. *Psychopharmacology, 190,* 269–319.

Millar, N. S., & Gotti, C. (2009). Diversity of vertebrate nicotinic acetylcholine receptors. *Neuropharmacology, 56,* 237–246.

Musso, F., Bettermann, F., Vucurevic, G., Stoeter, P., Konrad, A., & Winterer, G. (2007). Smoking impacts on prefrontal attentional network function in young adult brains. *Psychopharmacology (Berl), 191,* 159–169.

Newhouse, P., Kellar, K., Aisen, P., White, H., Wesnes, K., Coderre, E., … Levin, E. D. (2012). Nicotine treatment of mild cognitive impairment: A 6-month double-blind pilot clinical trial. *Neurology, 78,* 91–101.

Newhouse, P. A., Potter, A., & Singh, A. (2004). Effects of nicotinic stimulation on cognitive performance. *Current Opinion in Pharmacology, 4,* 36–46.

Ng, M., Freeman, M. K., Fleming, T. D., Robinson, M., Dwyer-Lindgren, L., Thomson, B., … Gakidou, E. (2014). Smoking prevalence and cigarette consumption in 187 countries, 1980–2012. *The Journal of the American Medical Association, 311,* 182–192.

Poltavski, D. V., Petros, T. V., & Holm, J. E. (2012). Lower, but not higher doses of transdermal nicotine facilitate cognitive performance in smokers on gender non preferred tasks. *Pharmacology, Biochemistry and Behavior, 102,* 423–433.

Poorthuis, R. B., Goriounova, N. A., Couey, J. J., & Mansvelder, H. D. (2009). Nicotinic actions on neuronal networks for cognition: General principles and long-term consequences. *Biochemical Pharmacology, 78,* 668–676.

Potter, A. S., & Newhouse, P. A. (2008). Acute nicotine improves cognitive deficits in young adults with attention-deficit/hyperactivity disorder. *Pharmacology, Biochemistry and Behavior, 88,* 407–417.

Shiffman, S., Dresler, C. M., Hajek, P., Gilburt, S. J. A., Targett, D. A., & Strahs, K. R. (2002). Efficacy of a nicotine lozenge for smoking cessation. *Archive of Internal Medicine, 162,* 1267–1276.

Swan, G. E., & Lessov-Schlagger, C. N. (2007). The effects of tobacco smoke and nicotine on cognition and the brain. *Neuropsychological Review, 17,* 259–273.

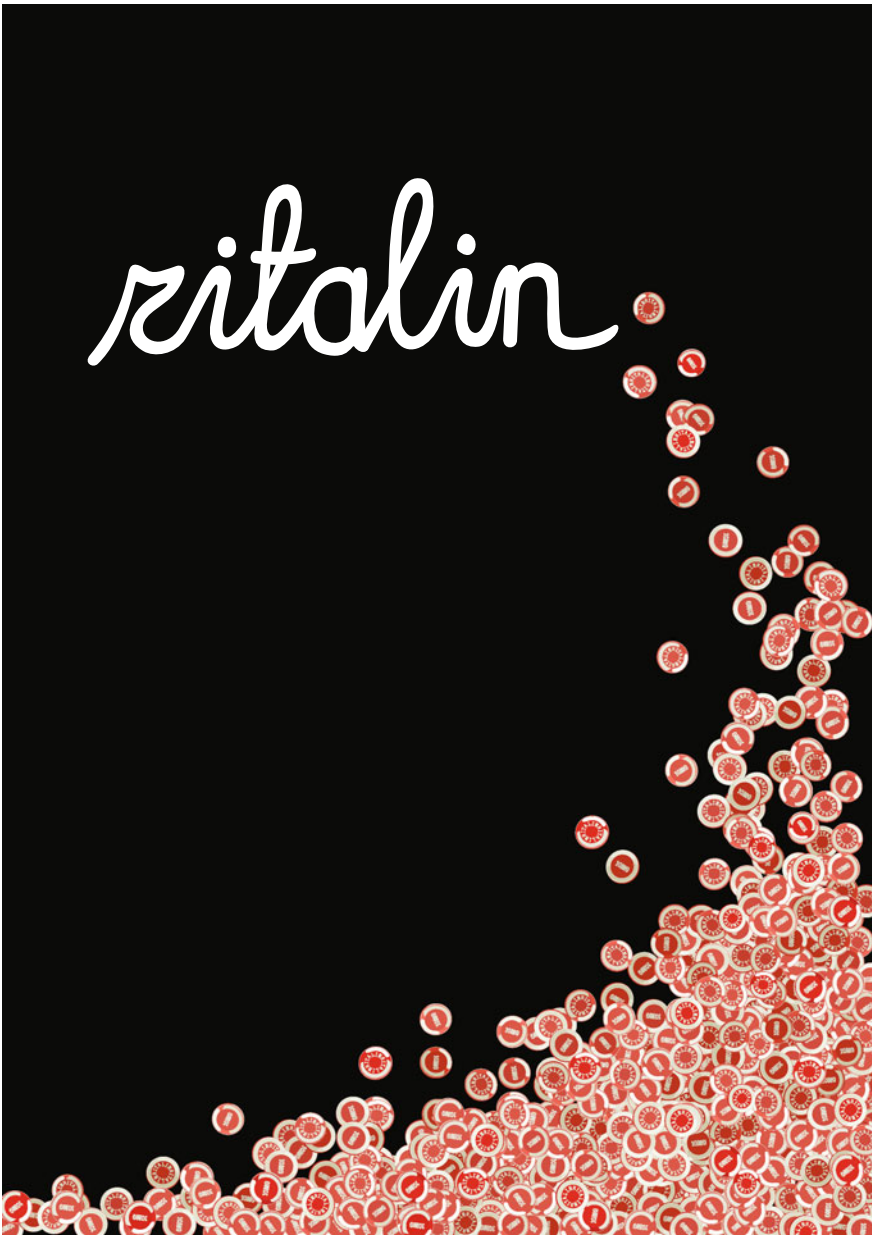
White, H. K., & Levin, E. D. (1999). Four-week nicotine skin patch treatment effects on cognitive performance in Alzheimer's disease. *Psychopharmacology (Berl), 143,* 158–165.

White, H. K., & Levin, E. D. (2004). Chronic transdermal nicotine patch treatment effects on cognitive performance in age-associated memory impairment. *Psychopharmacology (Berl), 171,* 465–471.

World Health Organization (2016). *World health statistics 2016.* Retrieved from http://www.who.int/gho/publications/world_health_statistics/2016/en/

Wu, J., Liui, Q., Yu, K., Hu, J., Kuo, Y. P., Segerberg, M., et al. (2006). Roles of nicotinic acetylcholine receptor beta subunits in function of human alpha4-containing nicotinic receptors. *Journal of Physiology, 576,* 103–118.

Wu, J., & Lukas, R. J. (2011). Naturally-expressed nicotinic acetylcholine receptor sub-types. *Biochemical Pharmacology, 82,* 800–807.


ritalin

Ritalin

Lorenza S. Colzato and Fréderique E. Arntz

Introduction

Methylphenidate, best known by its brand name Ritalin, is an amphetamine drug. Ritalin is the most prevalent medication for attention deficit/hyperactivity disorder (ADHD), a well-known psychiatric disorder characterized by hyperactivity and impulsivity. Ritalin increases the availability of dopamine (DA) and norepinephrine (NE) in the brain, especially affecting DA levels (Sulzer et al. 2005; Volkow et al. 2002a, b). DA is a catecholamine that innervates many regions throughout the brain (Moore and Bloom 1978) and is crucial in the regulation of attention and cognitive control (Cools and D'Esposito 2011; Colzato et al. 2010). Furthermore, DA is the precursor of NE so that the availability of DA also influences the NE levels in the brain indirectly. Given that the diagnosis of ADHD and the medical prescription of Ritalin have increased in the past decade, Ritalin has become more easily available to healthy population. Whereas Modafinil (see Chapter "Modafinil") has little evidence of dependence (Jasinski 2000), methylphenidate has a high risk of abuse (Morton and Stockton 2000).

Non-medical use of Ritalin and similar prescription drugs has expanded among healthy adults, especially college students. An "unofficial" way to obtain Ritalin is from family or friends who were prescribed with Ritalin. The most common reasons for trying Ritalin are to concentrate and perform better at work/study, to stay awake

L.S. Colzato (✉) · F.E. Arntz
Cognitive Psychology Unit and Leiden Institute for Brain and Cognition, Leiden University, Leiden, The Netherlands
e-mail: colzato@fsw.leidenuniv.nl

L.S. Colzato
Institute of Cognitive Neuroscience, Faculty of Psychology, Ruhr University Bochum, Bochum, Germany

L.S. Colzato, *Theory-Driven Approaches to Cognitive Enhancement*,
DOI 10.1007/978-3-319-57505-6_6

and to "get high" or to feel good. User statistics of nonmedical use of Ritalin differ widely as there are no official numbers available, because the use of Ritalin without prescription is nonregulated and is considered medication abuse. Therefore, the numbers vary considerably. McCabe et al. (2005) found 4.1% of students using Ritalin in the last academic year. In contrast to this finding, Low et al. (2002) found 35.5% of undergraduate students had used Ritalin as an enhancer in the past year. In another study, 3407 U.S. undergraduate college students were asked about the use of Ritalin in order to improve their cognitive performance (Rabiner et al. 2009). Of this sample 8.9% of the students reported use of Ritalin. Among these users 7.2% was male and 4.5% was female. Consistent with previous findings by McCabe et al. (2005), users were more often Caucasian than of other descendants (Afro-American, Hispanic, Asian). Two other factors that were associated with higher prevalence of Ritalin use were lower grades and membership of a sorority system (McCabe et al. 2005).

Given that Ritalin increases cognitive performance in individuals with ADHD (Mészáros et al. 2009; Faraone et al. 2004), in recent years the interest in the effectiveness of Ritalin as a potential cognitive enhancer in healthy individuals has increased. Unfortunately, the findings of studies investigating these effects have gained inconsistent or even contrasting results. The aim of this chapter is to provide an overview of the "state of the art" of the effects of Ritalin administration on cognition in healthy individuals, thereby clarifying whether it is advisable to use Ritalin as a cognitive enhancer.

In this chapter we will first describe how Ritalin administration affects DA function by taking into account genetic differences associated with baseline DA levels. Second, we will present an overview of the studies investigating the enhancing effects of Ritalin on cognitive functions in non-sleep-deprived healthy individuals. Third, we will review studies that address the effect of Ritalin in sleep-deprived individuals. Studies seem to suggest Ritalin increases working memory only to some extent and especially in challenging conditions.

Mechanisms of Action

Methylphenidate, the active ingredient of Ritalin, is a DA re-uptake inhibitor. That is, it increases DA and NE levels by blocking the transporters of these neurotransmitters (Sulzer et al. 2005; Volkow et al. 2001, 2002b), see Fig. 1. Consequently, because transport of DA is blocked, the amount of DA that is available postsynaptically is increased (Morton and Stockton 2000). The uptake peaks approximately between 60 and 180 min after ingestion, depending on the previously administered dose and individuals' differences in metabolism (Novartis 2016). It is generally recommended to take Ritalin after the consumption of food, as this not only reduces the occurrence of side effects, but also improves the rate at which Ritalin reaches its peak plasma levels (Chan et al. 1983). The effects last from 120 to approximately 240 min (Kimko et al. 1999), also depending on the

dosage and weight of the individual. The half-life of Ritalin is estimated to range around 3.5 h (Novartis 2016). An fMRI study from Volkow et al. (1998) found that peak brain levels are reached after 60 min after oral administration of Ritalin. Methylphenidate is first absorbed in the gastrointestinal tract and from there enters the body's circulation system (Kimko et al. 1999). Methylphenidate can cross the blood–brain barrier by a free diffusion mechanism of nonionized liphophilics. Given these properties, effects of methylphenidate occur shortly after ingestion of the medication (Pardridge and Connor 1973). This results in a rapid effect on dopaminergic supplies in the whole brain, especially increasing DA levels in the prefrontal cortex, which is crucial in the regulation of cognitive control (Cools and D'Esposito 2011; Colzato et al. 2010). The enhancing effects of cognitive control via Ritalin administration are assumed to be related to transporter blockade of the DAD1 receptor and the Alpha-2 adrenergic NE receptor (Spencer et al. 2015).

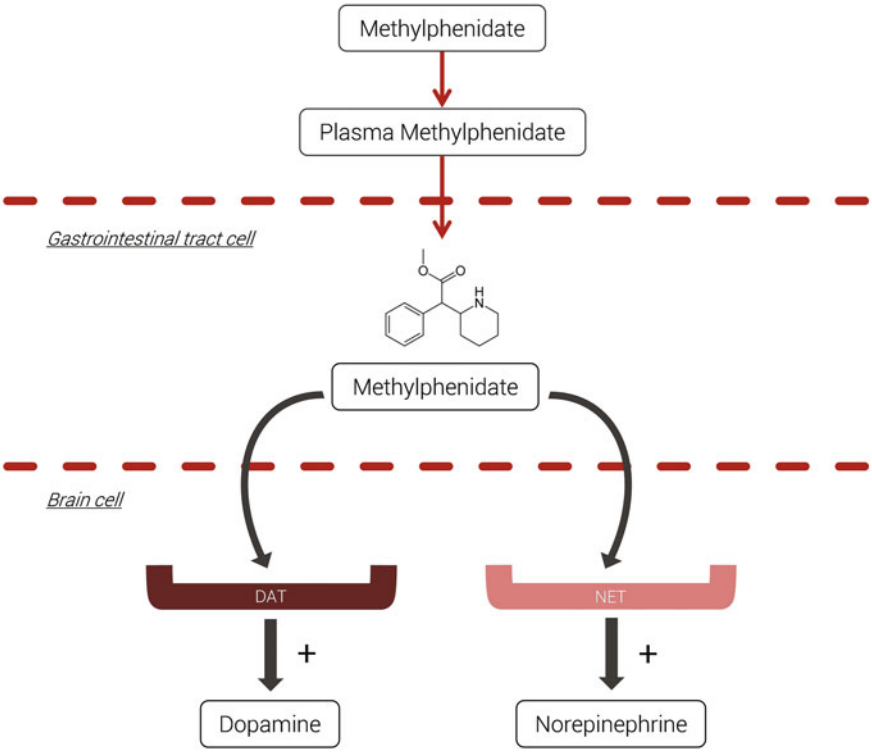


Fig. 1 Schematic representation of Ritalin metabolism. After ingestion Ritalin is absorbed in the gastrointestinal tract, enters the body's circulation system and crosses the blood brain barrier. There, Ritalin leads to blockage of the transporters of both dopamine (DAT) and norepinephrine (NET). This in turn leads to an increase in post-synaptic levels of dopamine and norepinephrine, especially in the prefrontal cortex

The medication has a dose-dependent relationship, with the recommended dose being 10–60 mg a day and the upper daily limit set at 1 mg/kg. This dosage is set for individuals with ADHD via clinical guidelines (Morton and Stockton 2000), however for healthy individuals there is no recommended dose available, as currently the use of Ritalin without prescription is not legal. Most studies investigating the effects of Ritalin on cognition in healthy individuals do not take the dose-dependent relationship into account, and are administering the same dose to all participants regardless of their weight. This methodological fallacy might be one factor contributing to inconsistent findings in the efficacy of Ritalin. Only few studies have taken this factor into account and worked with a mg/kg determined dose, ranging between 0.025 and 0.5 mg/kg (Volkow et al. 1999; Wetzel et al. 1981). Higher doses than 1 mg/kg/daily have been found to have detrimental effects including more pronounced side effects such as: insomnia, loss of appetite, nausea, nervousness, headaches, and high blood pressure (Rapport and Moffitt 2002). Some of the side effects are considered major given that they can cause heart rhythm abnormalities such as arrhythmia, tachycardia, and palpitations (Rappley 1997).

When Ritalin is used repeatedly over time, tolerance (i.e., a diminished response) may develop. Moreover, in contrast to tyrosine (see Chapter "Tyrosine"), the ingestion of a high dosage of Ritalin comes with the risk of overdose. Therefore, it is not surprising that misuse of Ritalin is associated with sudden death (Lakhan and Kirchgessner 2012). Even though for healthy individuals there is no recommended dose available, studies investigating this population typically use dosages between 5 and 60 mg (Repantis et al. 2010). Most studies investigating the enhancing effects of Ritalin administer a dose of 20 mg (Repantis et al. 2010). Beneficial or detrimental effects of Ritalin administration may depend on DA baseline level. These individual differences may be the crucial factor in explaining inconsistent findings of the effectiveness of Ritalin. More specifically, the effectiveness of amphetamines is influenced by genetic differences in a catechol-*O*-methyltranferase (COMT) enzyme (Mattay et al. 2003), which regulates the degradation of DA. This enzyme is genetically coded with two alleles, the valine (Val) and methionine (Met). The presence of a Val allele results in faster degradation of DA than the presence of a Met allele, resulting in less available DA in the brain (Caldù et al. 2007). As DA follows an inverted U-shaped function of effectivity (Cools and D'Esposito 2011), genetic carriers (Val/Val) associated with low DA baseline levels are the ones expected to profit the most from the administration of Ritalin. To date, one seminal study has taken these preexisting individual differences of baseline DA levels into account when investigating the effectiveness of amphetamine in healthy individuals. In an fMRI study, Mattay et al. (2003) explored the effect of the Val^{158}Met polymorphism (COMT gene) on the effectiveness of amphetamine in predicting working memory performance. Importantly, this study showed an enhancing effect of amphetamine administration in a working memory task only for Val/Val homozygotes (i.e., individuals potentially associated with lower frontal DA level). For Met/Met homozygotes (i.e., individuals potentially associated with higher frontal DA level), the amphetamine administration was found to have no effect when the workload of the working memory task was low or moderate and impaired performance at high working memory load.

Even if this hypothesis needs to be formally tested, given that Ritalin is pharmacologically very closely related to amphetamines, we speculate that genetic predisposition might modulate the effect of Ritalin in its role as cognitive enhancer.

Enhancement in Non-sleep-deprived Healthy Individuals

This section provides a summary of recent studies on the effect of Ritalin on healthy adults who are not sleep-deprived. In contrast to the animal literature, findings in humans were mixed. We will discuss factors that may be responsible for the contradictory results.

In animals, a recent review demonstrated a reliable enhancement of cognitive functions after the administration of Ritalin (Spencer et al. 2015). In particular, it seems that, following an inverted U-shaped function logic, low doses of Ritalin lead to improvement of cognitive functions related to prefrontal cortex (Berridge et al. 2006; Gamo et al. 2010). Spencer et al. (2015) suggested that these findings in animals may be translated to humans and, therefore, Ritalin could be regarded as a potential cognitive enhancer for healthy individuals.

Unfortunately, results from human literature do not support this idea and findings in healthy individuals are inconsistent. Ritalin seems to enhance cognitive functions related to memory only to some extent. At short term, a single dose of 20 or 40 mg can significantly augment declarative memory in a word-learning task, while lower doses (5 and 10 mg) induce no beneficial effects (Linssen et al. 2012). Moreover, a double-blind, placebo-controlled study by Camp-Bruno and Herting (1994) reported improved working memory after the ingestion of 20 mg Ritalin only on difficult tasks. Participants were tested 60 min after the administration of the medication. Improvement was found on the difficult task (Buschke Selective Reminding Test) that required selective remembering, whereas no effects on the free recall of words (Immediate and Delayed Free Recall) were found. Another study, employing a single dose of 20 mg, found no impact on the performance of a visual working memory task (Studer et al. 2010). Linssen et al. (2014) analyzed 60 studies in which the participants aged between 18 and 60 years were given a single dose of methylphenidate. Working memory was improved in 65% of the studies, followed by processing speed in 48%. Notably, less behavioral enhancement was evident for attention and vigilance (29%) and the improvement on problem solving and planning was even weaker. In particular the results that Ritalin does not really improve attention are surprising given that many healthy individuals taking Ritalin reported using it to enhance their focus of attention.

Another unexpected result is that even though administration of Ritalin enhanced inhibitory control in people suffering from ADHD (Schachar et al. 2008), this is not the case in healthy individuals. As indexed by the stop-signal task, a single dose of 45 mg did not improve the ability of stopping on time (Manza et al. 2016).

The enhancing effects of Ritalin administration in healthy individuals might not only depend on weight and on genetically determined differences, as discussed in the mechanism of action section, but they seem to depend on gender as well.

Women experienced more pronounced methylphenidate effects (Davis et al. 2012). These differences might arise from fluctuations in DA associated with the menstrual cycle, possibly due to estrogen. In line with this idea, D2 receptor availability varies according to the menstrual cycle (Czoty et al. 2009) and it has been proposed that cognitive functions associated with DA may depend on estrogen level (Colzato and Hommel 2014; Jacobs and Esposito 2011).

In sum, in healthy non-sleep-deprived individuals, Ritalin appears to increase working memory only to some extent and especially in challenging conditions.

Enhancing Effect in Sleep-Deprived Individuals

Because of its ability to increase wakefulness, in this section we will describe the only two studies exploring the effect of Ritalin on cognitive functions in sleep-deprived, but otherwise healthy adults. In contrast to the reliable effect of (see Chapter "Modafinil"), the few studies investigating the enhancing effects on cognition after sleep deprivation report inconsistent findings, with one study showing beneficial effects whereas the other failed to find any effects.

In a randomized, double-blind, placebo-controlled study, Bishop et al. (1997) found enhancing effects of repeated administration of a single dose of 10 mg Ritalin after 24 h of sleep deprivation. Ritalin was administered 2 h before testing, with an interval of 4 h in between doses. Results showed that Ritalin led to improved attention and vigilance performance. Furthermore, participants reported to be less tired and this increased alertness was supported by improvement on physiological measures of sleepiness. The alerting effect of Ritalin lasted up to 4 h after ingestion.

In contrast to the previous findings, Bray et al. (2004) found no enhancing effects in a randomized, double-blind, placebo-controlled study, where the effects of 20 mg Ritalin on verbal learning and executive functioning were tested after 24 h of sleep deprivation. The only notable effect that emerged was impairment of self-monitoring. That is, participants showed an overconfidence effect: their perceived performance was better than their actual performance on the tasks.

In sum, Ritalin does not seem to consistently enhance performance after sleep deprivation. The preliminary evidence that is available from the few studies that were carried out does seem to suggest an improvement of attention and vigilance of Ritalin administration after sleep deprivation, but at the cost of overconfidence.

Conclusion

As Ritalin increases DA levels in the prefrontal cortex, it has the potential to improve cognitive functioning. However, current research has found contradicting or inconsistent results. In non-sleep-deprived individuals, beneficial effects of moderate doses of Ritalin have been found on memory performance, but only to

some extent and especially in challenging conditions. It remains to be established whether these findings apply to the long-term administration of Ritalin. Hence, future studies assessing the impact of chronic Ritalin use and the risk of incurring potential side effects are necessary. Indeed, it needs to be clarified whether tolerance or even decline in performance will be encountered after the initial short-term enhancing effects on memory. Moreover, optimal protocols of administration in healthy individuals (e.g., dose of Ritalin dependent on weight, DA baseline levels and gender) still need to be identified.

Future studies need to shed light on whether the efficacy of Ritalin on working memory indeed depends on genetic markers of dopaminergic function. Given that Ritalin increases DA level in the brain, we speculate that Ritalin can promote cognitive performance whenever one has a lower than-optimal DA level. That is, depending on the initial DA baseline levels, some people may benefit more from Ritalin intake than others. This might explain why previous outcomes were mixed: some studies reported significant improvements, while others did not.

Further, more research is necessary in order to establish whether Ritalin has reliable enhancing effects after sleep deprivation as only few studies have addressed this topic.

In sum, considering the side effects and the abuse liability associated with Ritalin, the use of this drug does not seem to reliably enhance cognitive processes except working memory.

References

Berridge, C. W., Devilbiss, D. M., Andrzejewski, M. E., Arnsten, A. F., Kelley, A. E., Schmeichel, B., et al. (2006). Methylphenidate preferentially increases catecholamine neurotransmission within the prefrontal cortex at low doses that enhance cognitive function. *Biological Psychiatry, 60*(10), 1111–1120.

Bishop, C., Roehrs, T., Rosenthal, L., & Roth, T. (1997). Alerting effects of methylphenidate under basal and sleep-deprived conditions. *Experimental and Clinical Psychopharmacology, 5*(4), 344–352.

Bray, C. L., Cahill, K. S., Oshier, J. T., Peden, C. S., Theriaque, D. W., Flotte, T. R., et al. (2004). Methylphenidate does not improve cognitive function in healthy sleep-deprived young adults. *Journal of Investigative Medicine, 52*(3), 192–201.

Caldú, X., Vendrell, P., Bartrés-Faz, D., Clemente, I., Bargalló, N., Jurado, M. Á., et al. (2007). Impact of the COMT Val 108/158 Met and DAT genotypes on prefrontal function in healthy subjects. *Neuroimage, 37*(4), 1437–1444.

Camp-Bruno, J. A., & Herting, R. L. (1994). Cognitive effects of milacemide and methylphenidate in healthy young adults. *Psychopharmacology (Berl), 115*(1–2), 46–52.

Chan, Y. P. M., Swanson, J. M., Soldin, S. S., Thiessen, J. J., Macleod, S. M., & Logan, W. (1983). Methylphenidate hydrochloride given with or before breakfast: II. Effects on plasma concentration of methylphenidate and ritalinic acid. *Pediatrics, 72*(1), 56–59.

Colzato, L. S., & Hommel, B. (2014). Effects of estrogen on higher-order cognitive functions in unstressed human females may depend on individual variation in dopamine baseline levels. *Frontiers in Neuroscience, 8,* 65.

Colzato, L. S., Waszak, F., Nieuwenhuis, S., Posthuma, D., & Hommel, B. (2010). The flexible mind is associated with the catechol-*O*-methyltransferase (COMT) Val 158 Met

polymorphism: Evidence for a role of dopamine in the control of task-switching. *Neuropsychologia, 48*(9), 2764–2768.

Cools, R., & D'Esposito, M. (2011). Inverted-U-shaped dopamine actions on human working memory and cognitive control. *Biological Psychiatry, 69*(12), 113–125.

Czoty, P. W., Riddick, N. V., Gage, H. D., Sandridge, M., Nader, S. H., Garg, S., et al. (2009). Effect of menstrual cycle phase on dopamine D2 receptor availability in female cynomolgus monkeys. *Neuropsychopharmacology, 34,* 548–554.

Davis, C., Fattore, L., Kaplan, A. S., Carter, J. C., Levitan, R. D., & Kennedy, J. L. (2012). The suppression of appetite and food consumption by methylphenidate: The moderating effects of gender and weight status in healthy adults. *International Journal of Neuropsychopharmacology, 15*(2), 181–187.

Faraone, S. V., Spencer, T., Aleardi, M., Pagano, C., & Biederman, J. (2004). Meta-analysis of the efficacy of methylphenidate for treating adult attention-deficit/hyperactivity disorder. *Journal of Clinical Psychopharmacology, 24*(1), 24–29.

Gamo, N. J., Wang, M., & Arnsten, A. F. (2010). Methylphenidate and atomoxetine enhance prefrontal function through α 2-adrenergic and dopamine D 1 receptors. *Journal of the American Academy of Child and Adolescent Psychiatry, 49*(10), 1011–1023.

Jacobs, E., & Esposito, M. D. (2011). Estrogen shapes dopamine-dependent cognitive processes: Implications for women's health. *Journal of Neuroscience, 31,* 5286–5293.

Jasinski, D. R. (2000). An evaluation of the abuse potential of Modafinil using methylphenidate as a reference. *Journal of Psychopharmacology, 14*(1), 53–60.

Kimko, H. C., Cross, J. T., & Abernethy, D. R. (1999). Pharmacokinetics and clinical effectiveness of methylphenidate. *Clinical Pharmacokinetics, 37*(6), 457–470.

Lakhan, S. E., & Kirchgessner, A. (2012). Prescription stimulants in individuals with and without attention deficit hyperactivity disorder: Misuse, cognitive impact, and adverse effects. *Brain and Behavior, 2*(5), 661–677.

Linssen, A. M. W., Sambeth, A., Vuurman, E. F. P. M., & Riedel, W. J. (2014). Cognitive effects of methylphenidate in healthy volunteers: A review of single dose studies. *International Journal of Neuropsychopharmacology, 17*(6), 961–977.

Linssen, A. M. W., Vuurman, E. F. P. M., Sambeth, A., & Riedel, W. J. (2012). Methylphenidate produces selective enhancement of declarative memory consolidation in healthy volunteers. *Psychopharmacology (Berl), 221*(4), 611–619.

Low, K. G., & Gendaszek, A. E. (2002). Illicit use of psychostimulants among college students: A preliminary study. *Psychology, Health & Medicine, 7,* 283–287.

Manza, P., Hu, S., Ide, J. S., Farr, O. M., Zhang, S., Leung, H. C., et al. (2016). The effects of methylphenidate on cerebral responses to conflict anticipation and unsigned prediction error in a stop-signal task. *Journal of Psychopharmacology, 30,* 283–293.

Mattay, V. S., Goldberg, T. E., Fera, F., Hariri, A. R., Tessitore, A., Egan, M. F., et al. (2003). Catechol *O*-methyltransferase val158-met genotype and individual variation in the brain response to amphetamine. *Proceedings of the National Academy of Sciences, 100*(10), 6186–6191.

McCabe, S. E., Knight, J. R., Teter, C. J., & Wechsler, H. (2005). Non-medical use of prescription stimulants among US college students: Prevalence and correlates from a national survey. *Addiction, 100*(1), 96–106.

Mészáros, Á., Czobor, P., Bálint, S., Komlósi, S., Simon, V., & Bitter, I. (2009). Pharmacotherapy of adult attention deficit hyperactivity disorder (ADHD): A meta-analysis. *The International Journal of Neuropsychopharmacology, 12*(8), 1137–1147.

Moore, R. Y., & Bloom, F. E. (1978). Central catecholamine neuron systems: Anatomy and physiology of the dopamine systems. *Annual Review of Neuroscience, 1*(1), 129–169.

Morton, W. A., & Stockton, G. G. (2000). Methylphenidate abuse and psychiatric side effects. *Primary Care Companion to the Journal of Clinical Psychiatry, 2,* 159–164.

Novartis (2016). *Ritalin LA® prescribing information*. Retrieved from: https://www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/files/ritalin_la.pdf

Pardridge, W. M., & Connor, J. D. (1973). Saturable transport of amphetamine across the blood–brain barrier. *Cellular and Molecular Life Sciences, 29*(3), 302–304.

Rabiner, D. L., Anastopoulos, A. D., Costello, E. J., Hoyle, R. H., McCabe, S. E., & Swartzwelder, H. S. (2009). Motives and perceived consequences of nonmedical ADHD medication use by college students are students treating themselves for attention problems? *Journal of Attention Disorders, 13*(3), 259–270.

Rappley, M. D. (1997). Safety issues in the use of methylphenidate. *Drug Safety, 17,* 143–148.

Rapport, M. D., & Moffitt, C. (2002). Attention deficit/hyperactivity disorder and methylphenidate: A review of height/weight, cardiovascular, and somatic complaint side effects. *Clinical Psychology Review, 22*(8), 1107–1131.

Repantis, D., Schlattmann, P., Laisney, O., & Heuser, I. (2010). Modafinil and methylphenidate for neuroenhancement in healthy individuals: A systematic review. *Pharmacological Research, 62,* 187–206.

Schachar, R., Ickowicz, A., Crosbie, J., Donnelly, G. A., Reiz, J. L., Miceli, P. C., … Darke, A. C. (2008). Cognitive and behavioral effects of multilayer-release methylphenidate in the treatment of children with attention-deficit/hyperactivity disorder. *Journal of Child and Adolescent Psychopharmacology*, *18*(1), 11–24.

Spencer, R. C., Devilbiss, D. M., & Berridge, C. W. (2015). The cognition-enhancing effects of psychostimulants involve direct action in the prefrontal cortex. *Biological Psychiatry, 77*(11), 940–950.

Studer, P., Wangler, S., Diruf, M., Kratz, O., Moll, G., & Heinrich, H. (2010). ERP effects of methylphenidate and working memory load in healthy adults during a serial visual working memory task. *Neuroscience Letters, 482*(2), 172–176.

Sulzer, D., Sonders, M. S., Poulsen, N. W., & Galli, A. (2005). Mechanisms of neurotransmitter release by amphetamines: A review. *Progress in Neurobiology, 75*(6), 406–433.

Volkow, N. D., Fowler, J. S., Wang, G. J., Ding, Y. S., & Gatley, S. J. (2002a). Role of dopamine in the therapeutic and reinforcing effects of methylphenidate in humans: Results from imaging studies. *European Neuropsychopharmacology, 12*(6), 557–566.

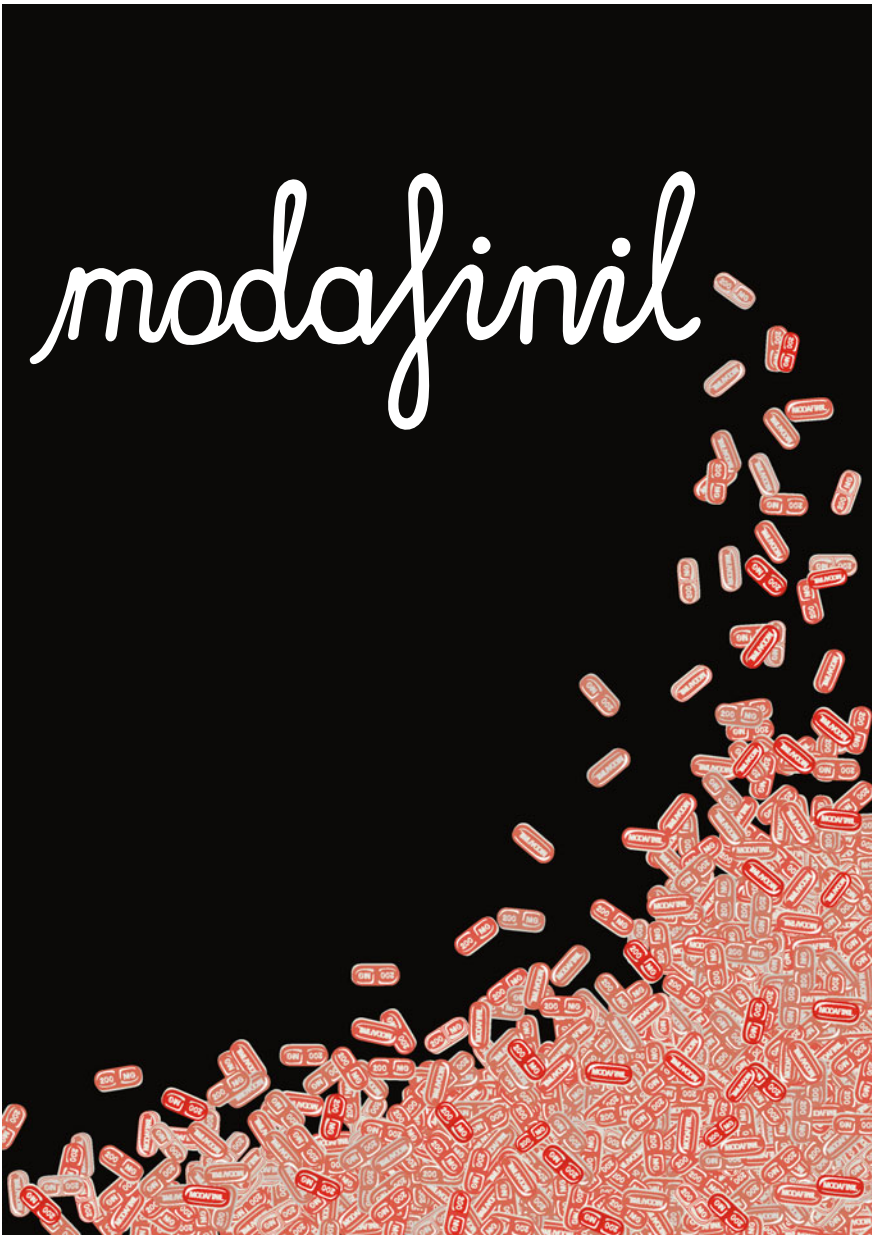
Volkow, N. D., Fowler, J. S., Wang, G., Ding, Y., & Gatley, S. J. (2002b). Mechanism of action of methylphenidate: Insights from PET imaging studies. *Journal of Attention Disorders, 6,* 31–44.

Volkow, N. D., Wang, G. J., Fowler, J. S., Gatley, S. J., Logan, J., Ding, Y. S., et al. (1998). Dopamine transporter occupancies in the human brain induced by therapeutic doses of oral methylphenidate. *American Journal of Psychiatry, 155*(10), 1325–1331.

Volkow, N. D., Wang, G. J., Fowler, J. S., Logan, J., Gatley, S. J., Wong, C., et al. (1999). Reinforcing effects of psychostimulants in humans are associated with increases in brain dopamine and occupancy of D2 receptors. *Journal of Pharmacology and Experimental Therapeutics, 291*(1), 409–415.

Volkow, N. D., Wang, G., Fowler, J. S., Logan, J., Gerasimov, M., Maynard, L., et al. (2001). Therapeutic doses of oral methylphenidate significantly increase extracellular dopamine in the human brain. *The Journal of Neuroscience, 21*(2), 1–5.

Wetzel, C. D., Squire, L. R., & Janowsky, D. S. (1981). Methylphenidate impairs learning and memory in normal adults. *Behavioral and Neural Biology, 31*(4), 413–424.


modafinil

Modafinil

Lorenza S. Colzato and Rebecca Mourits

Introduction

The atypical psychostimulant Modafinil is a drug that promotes wakefulness. For this reason, it is often used in the treatment of sleeping disorders such as narcolepsy and shift sleeping disorder. Modafinil belongs to a group of drugs named "eugeroic." These drugs mimic the effects of amphetamines by promoting the maintenance of wakefulness, but do so without the negative side effects typically associated with amphetamines (Whitmore et al. 2006; Minzenberg and Carter 2008; Mereu et al. 2013). Whereas amphetamines have a high risk of abuse (Kollins et al. 2001), Modafinil has fewer, milder side effects, and little evidence of dependence (Jasinski 2000).

Modafinil promotes a number of neurochemical actions that may be related to primary effects on catecholaminergic systems (Madras 2006). Given that these primary effects on catecholaminergic systems are generally beneficial in improving cognitive functions, the efficacy of Modafinil administration as a way to enhance cognition has been studied under different circumstances. As Modafinil appears to be a candidate for enhancing cognitive function with very low abuse liability, it has already been introduced in various professions requiring prolonged wakefulness, such as workers in the forced army and health care. Indeed, approximately 90% of Modafinil users are healthy individuals with no sleep disorders aiming to enhance their attentional capacity (Baranski et al. 2004). Therefore, it is not surprising that Modafinil is mostly used by healthy on-call physicians and people within academia

L.S. Colzato (✉) · R. Mourits
Cognitive Psychology Unit and Leiden Institute for Brain and Cognition, Leiden University, Leiden, The Netherlands
e-mail: colzato@fsw.leidenuniv.nl

L.S. Colzato
Institute of Cognitive Neuroscience, Faculty of Psychology, Ruhr University Bochum, Bochum, Germany

L.S. Colzato, *Theory-Driven Approaches to Cognitive Enhancement*,
DOI 10.1007/978-3-319-57505-6_7

(Franke et al. 2013; Greely 2008). Given, the nature of people working in the army and health care and the safety of the people involved, thorough and meticulous research on Modafinil and how it affects cognitive processes of healthy adults is crucial. However, to date, both the mechanism of action and the effectiveness of Modafinil on brain and cognition are not yet well understood. This chapter provides a summary of the existing studies exploring how Modafinil administration affects cognitive processes in healthy adults. The aim of this chapter is to create better understanding of the circumstances under which Modafinil has a positive effect on cognition and to clarify whether the drug is indeed useful as a cognitive enhancer.

First, this chapter describes the mechanism of action thorough which Modafinil administration affects cognitive-enhancing mechanisms in the brain. Second, an overview of the available studies investigating the effect of Modafinil on cognitive performance of healthy non-sleep-deprived individuals will be given. For these people, Modafinil appears to increase specifically attention and cognitive control and this effect seems to be more pronounced in challenging task conditions and in low performing individuals. Lastly, studies investigating the effect of Modafinil on sleep-deprived individuals will be reviewed. In these people, Modafinil seems to maintain and restore performance on cognitive tasks, but at the possible costs of subjective overconfidence.

Mechanism of Action

Modafinil is synthesized from adrafinil, a psychostimulant used to promote vigilance (Fontan et al. 1990). When administered in single oral doses, plasma concentrations of Modafinil peak approximately 2.5 h after intake (McClellan and Spencer 1998; Keating and Raffin 2005). The half-time elimination (time necessary for plasma concentration of a drug to drop to 50% during the elimination phase) is approximately 12–15 h. After oral administration, Modafinil is primarily transformed in the liver to inactive metabolites (the minor metabolite Modafinil acid and major metabolite Modafinil sulphone), which are then excreted in the urine (Moachon et al. 1996). The pharmakinetics of Modafinil are linear for the doses ranging 200 and 600 mg and the terminal half-life (time necessary to eliminate 50% of the drug from the body) is 9–14 h (Whitmore et al. 2006; Mereu et al. 2013).

Unfortunately, the specific mechanism of action of Modafinil is not yet well understood (Ballon and Fiefel 2006). The administration of Modafinil has been found to increase levels of serotonin, extracellular dopamine (DA), glutamate, noradrenaline (NE), histamine, and orexin in various brain regions, but to decrease extracellular GABA (Minzenberg and Carter 2008). It has been suggested that both increased dopaminergic and noradrenergic transmission and decreased GABAergic activity may play important roles in the positive effect the psychostimulant has on wakefulness (Baranskiet al. 2004). Mechanistic studies of Modafinil have frequently focused on the involvement of the dopamine transporter (DAT) and norepinephrine transporter (NET) (Dunn et al. 2012; Louvet et al. 2012; Funayama et al. 2014). Modafinil binds to the DAT and NET. This results in a direct increase

of extracellular DA and NE and in an indirect rise of serotonin, glutamate, and histamine levels, while simultaneously decreasing GABA levels, see Fig. 1 (Mereu et al. 2013; Minzenberg and Carter 2008). As the effect of Modafinil on the release of DA in the nucleus accumbens is weak and dose-dependent, the probability of drug overdose, abuse, and tolerance is very small.

The recommended daily dose of Modafinil is 200–400 mg, given once or twice a day. Modafinil seems to be well tolerated with little side effects, the tolerability profiles of 200–400 mg doses are generally similar to that of placebo (McClellan

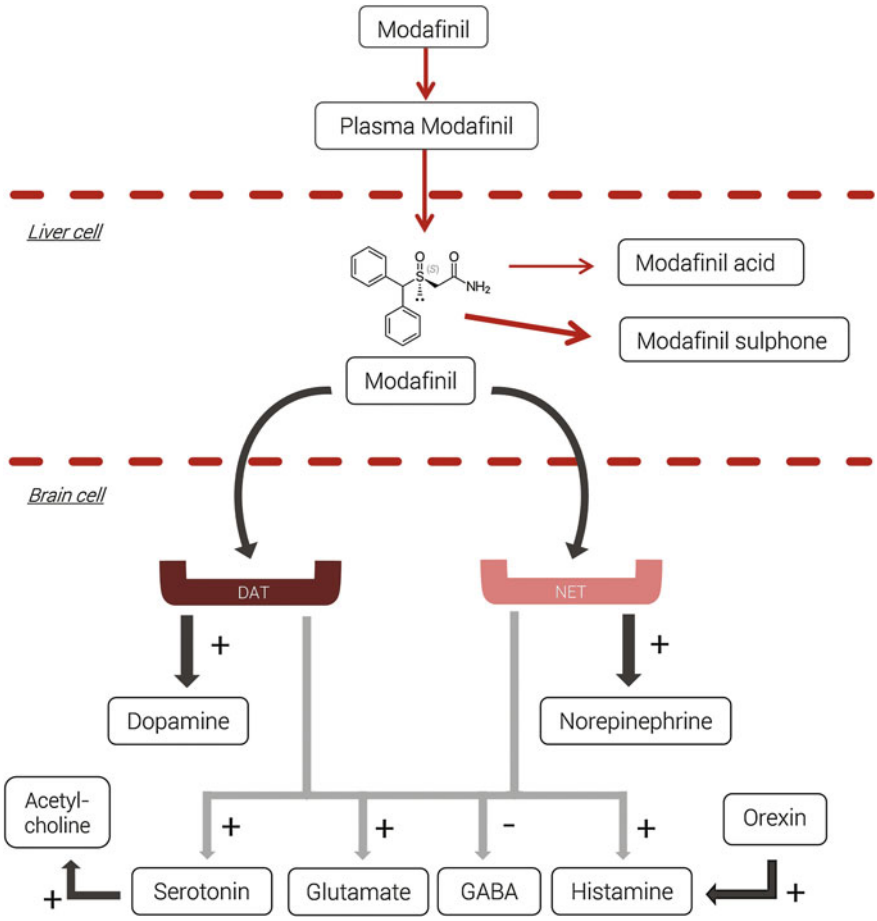


Fig. 1 Schematic representation of Modafinil metabolism. In the liver Modafinil is transformed to inactive metabolites: Modafinil acid and Modafinil sulphone. After having crossed the blood–brain barrier, Modafinil binds to the dopamine transporter (DAT) and norepinephrine transporter (NET). This result in a direct increase of extracellular dopamine and norepinephrine and in an indirect rise of serotonin, glutamate, acetylcholine, histamine, and Orexin levels, while simultaneously decreasing GABA levels

and Spencer 1998). However, higher doses of 400–600 mg may cause headache, nervousness, dizziness, or nausea. Other possible side effects, such as increased urinary frequency, hypertension, and hallucination, are rarely found.

Enhancing Effect in Healthy Non-sleep-Deprived Individuals

Although originally used for the treatment of narcolepsy and other sleep disorders, but given that users are mostly healthy individuals, Modafinil has become the focus of scientific interest for its allegedly cognitive-enhancing properties. This section provides an overview of recent studies on the effect of Modafinil on healthy adults who are not sleep-deprived. Given some findings were mixed, we will discuss factors that may be responsible for the contradictory results.

Several studies indicate that Modafinil enhances various cognitive functions, primarily those that highly depend on cognitive control and processes involving the prefrontal cortex (Geng et al. 2013). These beneficial effects include improvements in planning and decision-making, working memory, inhibitory control, and proactive cognitive control. For instance, a placebo-controlled, randomized, single-dose study evaluated the cognitive enhancement potential of Modafinil using a battery of neuropsychological tests (Turner et al. 2003). Sixty adults were given a single dose of either 100 or 200 mg. In general, the effects were not dose-dependent, that is, the higher dose of Modafinil did not induce better performance, with the only exception of inhibitory control (as indexed by the stop-signal task). The study showed that Modafinil selectively augments performance on spatial planning, visual recognition memory, response inhibition, and working memory (as indexed by the digit span). However, there was no beneficial effect on spatial memory, attentional set-shifting and rapid visual information processing. This selective effect of Modafinil may be explained by the fact that the effectiveness of Modafinil may dependent on the level of task difficulty. Several studies indicate that the beneficial effects of Modafinil were most prominent or even solely present when the difficulty of the tasks was high (Müller et al. 2013; Marchant et al. 2009). This indicates that Modafinil may primarily increase performance in non-sleep-deprived individuals but only when tasks are rather challenging.

One retrospective analysis study (n = 89), combining two earlier studies on the effectiveness of Modafinil on a battery of cognitive tests in healthy university students (Randall et al. 2005), found that the effectiveness of Modafinil depends on the individual performance baseline levels (as indexed by IQ). The results indicated both doses of 100 and of 200 mg improved response speed and target sensitivity in a sustained attention test, but only for individuals with lower IQ. This suggests that primarily suboptimal performing individuals can benefit from Modafinil intake. Consistent with these findings on attention, the beneficial effect of Modafinil on

working memory was also limited to participants that originally exhibited poorer baseline performance (Müller et al. 2004).

In some cases, Modafinil seems to have adverse effects on higher order cognitive processes. Modafinil was found to impair creativity in terms of convergent thinking especially in participants who were highly creative, whereas it reduced divergent thinking in all participants (Mohamed 2014). However, a double-blind, placebo-controlled study by Müller et al. (2013) replicated beneficial effects of Modafinil administration on planning, memory, and decision-making only in the most demanding conditions, but failed to find any effects on creativity.

In sum, in healthy non-sleep-deprived individuals, Modafinil appears to increase specifically attention and cognitive control and this effect seems to be more pronounced in challenging task conditions and in low performing individuals.

Enhancing Effect in Healthy Sleep-Deprived Individuals

In this section, we will review studies investigating the effect of Modafinil on cognitive functions in sleep-deprived, but otherwise healthy adults. These studies involve sleep deprivation ranging in their total period from 40 to 85 h and typically fall into one of two categories: maintenance and recuperation. In maintenance studies, participants are given smaller doses on a more frequent basis, for example, 100–200 mg every set amount of hours. The aim here is to determine if cognitive performances are maintained throughout a period of wakefulness. In recuperation studies, participants are typically administered a single, larger dose, e.g., 300–400 mg, after becoming extremely fatigued due to lack of sleep. The aim is to determine if cognitive performances can be restored to or near baseline levels.

One placebo-controlled, double-blind maintenance study on six healthy volunteers examined cognitive performance in terms of speed and accuracy in detecting a target using the visual search paradigm (Stivalet et al. 1998). Modafinil was administered three times a day in doses of 100 mg during 60 h of sleep deprivation. The results indicated Modafinil compensated for the slowing of serial processes and the increase of errors due to sleep deprivation. The relative effects of three different doses of Modafinil were examined during a sleep deprivation period of 64 h in a third double-blind, placebo-controlled maintenance study (Baranski et al. 1998). A dose-related effect was found: a total dose of 300 mg in a 24 h period, administered as 100 mg every 8 h, kept cognitive performance near or even at baseline levels; 150 mg of Modafinil, administered as 50 mg every 8 h, maintained performance to a lesser degree; 50 mg administered as 16.7 mg every 8 h did not substantially differ from the placebo.

Further, a seminal study by Bodenmann et al. (2009) showed that effects of Modafinil on waking functions after sleep loss are determined by catechol-O-methyltransferase (COMT) genotype. COMT is an enzyme that catalyzes the breakdown of DA in the cerebral cortex. Given that Modafinil increases DA level in the brain, the authors investigated whether the functional $Val^{158}Met$

polymorphism contributes to individual differences in the reactivity to Modafinil administration. The findings revealed that Val/Val homozygotes (i.e., individuals potentially associated with lower frontal DA level) showed larger beneficial effects of Modafinil administration than Met/Met homozygotes (i.e., individuals potentially associated with higher frontal DA level), suggesting that genetically determined differences in DA function may explain inter-individual differences in response to Modafinil administration.

Most research on Modafinil as a potential cognitive enhancer in healthy sleep-deprived people has been conducted in controlled laboratory conditions. However, given that Modafinil is often used by workers in the military and health care, who need to stay awake for prolonged periods of time, there is the need for field research or studies highly simulating real-life situations. This is particularly important given that these professions directly involve the safety not only of the individuals taking Modafinil but also of others. Caldwell et al. (2000) conducted one such study, focused on sustaining alertness and performance of six aviators. Throughout two 40 h periods of wakefulness, they were administered either three 200 mg doses or a placebo and their performances on a helicopter simulation flight were evaluated. Modafinil sustained both alertness and performance on four out of six flight maneuvers, especially in the time-span when fatigue was at the highest peak. The drug effects became more prominent as the period of sleep deprivation increased, a finding consistent with those by Lagarde and Batéjat (1995) and Pigeau et al. (1995). However, side effects such as nausea were more notable in this study, possibly due to the moving aspect of the flight simulation. Another placebo-controlled field study was conducted by Whitmore et al. (2006). Subjects participated in a simulated escape and evasion scenario and were administered doses of either 100 or 200 mg every 8 h during an 88 h period of wakefulness. Modafinil maintained cognitive performance, measured by math accuracy, during this period. These results were in line with an earlier field study by Whitmore et al. (2004) that was specifically set up to simulate the environment and workload that aircrew or special forces workers may experience during military ground operations.

Even though the results of studies described above plead in favor of the use of Modafinil as cognitive enhancer considering its low abuse risk and side effects, other findings suggest more cautious conclusions. Indeed, the drug may influence self-monitoring and metacognitive abilities. Recently, Mohamed (2015) proposed the idea that Modafinil did not enhance or maintain cognitive functions per se but it augments the individual perceived confidence and judgment in her/his own performance. Even though task performance may be objectively not improved, the overconfidence effect may be achieved by the increased salience of pleasure in performing such tasks under the influence of Modafinil. In line with this idea, Baranski and Pigeau (1997) reported that a single 300 mg dose of Modafinil, administered to individuals who were deprived of sleep in a recuperative paradigm, induced an overconfidence effect: subjects' estimates of their own cognitive performance exceeded their actual performance. In other words, the capability to assess one's own performance accurately may be negatively affected through the use of

Modafinil. This is in line with another study (Batejat and Lagarde 1999) reporting Modafinil to cause similar changes in self-confidence. A placebo-controlled study investigating driving simulator performance (Gurtman et al. 2008) also found that Modafinil may induce overconfidence in driving ability. The drug was administered as a single dose of 300 mg and increased subjective judgements of driving performance after participants remained awake overnight. However, a maintenance study that administered the drug in several smaller doses of 100 mg (Baranski et al. 2002) found no evidence of overconfidence. The overconfidence effect was also not found in a study on healthy, non-sleep-deprived individuals, even though participants in the Modafinil condition did overall display a nonsignificant tendency toward boldness in their judgement on their performance on the cognitive tests (Baranski et al. 2004). This indicates that the overconfidence effect may be a relative dose-dependent side effect (i.e., probable to appear only with high doses) that is present more in sleep-deprived individuals than in healthy, non-sleep-deprived individuals.

In sum, administration of Modafinil shows promising potential to maintain cognitive function in sleep-deprived individuals: however, caution may be needed given a possible overconfidence effect.

Conclusion

As it binds to DAT and NET, Modafinil has the potential to impact primarily the dopaminergic and noradrenergic system and secondarily other neurotransmitters critically relevant for cognitive functioning such as GABA. Even though more research is necessary to further elucidate the neurobiological underpinnings underlying the effect of Modafinil on cognition, in non-sleep-deprived healthy individuals Modafinil seems to improve mainly attention and cognitive control in challenging conditions and this effect seems to be limited to suboptimal performing individuals. Consequently, future studies that explore the cognitive-enhancing effects of Modafinil should consider individual variations in baseline performance.

In healthy sleep-deprived individuals Modafinil seems to maintain and restore performance on cognitive tasks, but at the possible costs of subjective overconfidence. That is, the use of Modafinil, especially in military and medical settings, raises significant ethical issues given that this drug augments the individual perceived confidence and judgment in her/his own performance. Accordingly, future studies need to shed light on the safety and efficiency of the administration of Modafinil and whether this drug increases human errors in decision-making in naturalistic environment.

Moreover, the effectivity of Modafinil seems to be determined by the COMT genotype. Future studies investigating the effect of Modafinil on cognition should consider genetic markers associated with DA availability in the brain. Indeed, genetic carriers associated with low DA baseline levels are the ones expected to profit the most from the administration of Modafinil. Therefore, we suggest that

genetic predisposition might modulate the effect of Modafinil in its role as cognitive enhancer.

In sum, even if more research is required, given its low liability to abuse and little side effects, Modafinil seems a promising tool for enhancing cognition.

References

Ballon, J. S., & Feifel, D. (2006). A systematic review of Modafinil: Potential clinical uses and mechanisms of action. *Journal of Clinical Psychiatry, 67*(4), 554–566.

Baranski, J. V., Cian, C., Esquivié, D., Pideau, R. A., & Raphel, C. (1998). Modafinil during 64 h of sleep deprivation: Dose-related effects on fatigue, alertness, and cognitive performance. *Military Psychology, 10*(3), 173–193.

Baranski, J. V., Gil, V., McLellan, T., Moroz, D., Buguet, A., & Radomskir, M. (2002). Effects of Modafinil on cognitive performance during 40 hours of sleep deprivation in a warm environment. *Military Psychology, 14,* 23–48.

Baranski, J. V., & Pigeau, R. (1997). Self-monitoring cognitive performance during sleep deprivation: Effects of Modafinil, D-amphetamine and placebo. *Journal of Sleep Research, 6,* 84–91.

Baranski, J. V., Pigeau, R., Dinich, P., & Jacobs, I. (2004). Effects of Modafinil on cognitive and meta-cognitive performance. *Human Psychopharmacology: Clinical and Experimental, 19,* 323–332.

Batejat, D., & Lagarde, D. (1999). Naps and Modafinil as countermeasures for the effects of sleep deprivation on cognitive performance. *Aviation, Space and Environmental Medicine, 70*(5), 493–498.

Bodenmann, S., Xu, S., Luhmann, U. F. O., Arand, M., Berger, W., Jung, H. H., et al. (2009). Pharmacogenetics of Modafinil after sleep loss: Catechol-*O*-methyltransferase genotype modulates waking functions but not recovery sleep. *Clinical Pharmacology and Therapeutics, 85*(3), 296–304.

Caldwell, J. A., Jr., Caldwell, J. L., Smyth, N. K., III, & Hall, K. K. (2000). A double-blind, placebo-controlled investigation of the efficacy of modafinil for sustaining the alertness and performance of aviators: A helicopter simulator study. *Psychopharmacology (Berl), 150*(3), 272–282.

Dunn, D., Hostetler, G., Iqbal, M., Messina-McLaughlin, P., Reiboldt, A., Lin, Y. G.,… & Chatterjee, S. (2012). Wake-promoting agents: Search for next generation Modafinil: Part I. *Bioorganic & Medicinal Chemistry Letters, 22*, 2312–2314.

Fontan, B., Fontarai, J., Micas, M., & Albarede, J. L. (1990). Value of computerized psychometric evaluation in the assessment of the activity of Olmifon (adrafinil) on alertness and cognitive performance in elderly retirement home patients. *Psychologie Medicale, 22,* 253–267.

Franke, A. G., Bagusat, C., Dietz, P., Hoffmann, I., Simon, P., Ulrich, R., et al. (2013). Use of illicit and prescription drugs for cognitive or mood enhancement among surgeons. *BMC Medicine, 11*(1), 1.

Funayama, T., Ikeda, Y., Tateno, A., Takahashi, H., Okubo, Y., Fukayama, H., et al. (2014). Modafinil augments brain activation associated with reward anticipation in the nucleus accumbens. *Psychopharmacology (Berl), 231,* 3217–3228.

Geng, J. J., Soosman, S., Sun, Y., DiQuattro, N. E., Stankevitch, B., & Minzenberg, M. J. (2013). A match made by Modafinil: Probability matching in choice decisions and spatial attention. *Journal of Cognitive Neuroscience, 25*(5), 657–669.

Greely, H., Sahakian, B., Harris, J., Kessler, R. C., Gazzaniga, M., Campbell, P., et al. (2008). Towards responsible use of cognitive-enhancing drugs by the healthy. *Nature, 456*(7223), 702–705.

Gurtman, C. G., Broadbear, J. H., & Redman, J. R. (2008). Effects of Modafinil on simulator driving and self-assessment of driving following sleep deprivation. *Human Psychopharmacology: Clinical and Experimental, 23,* 681–692.

Jasinski, D. R. (2000). An evaluation of the abuse potential of Modafinil using methylphenidate as a reference. *Journal of Psychopharmacology, 14*(1), 53–60.

Keating, G. M., & Raffin, M. J. (2005). Modafinil. *CNS Drugs, 19*(9), 785–803.

Kollins, S. H., MacDonald, E. K., & Rush, C. R. (2001). Assessing the abuse potential of methylphenidate in nonhumans and human subjects: A review. *Pharmacology, Biochemistry and Behavior, 68,* 611–627.

Lagarde, D., & Batejat, D. (1995). Some measures to reduce effects of prolonged sleep deprivation. *Clinical Neurophysiology, 25*(6), 376–385.

Louvet, P., Schweizer, D., Gourdel, M., Riguet, E., Yue, C., Marcy, V. R.,… & Chatterjee, S. (2012). Wake-promoting agents: Search for next generation Modafinil: Part IV. *European Journal of Medicinal Chemistry, 54*, 949–951.

Madras, B. K., Xie, Z., Lin, Z., Jassen, A., Panas, H., Lynch, L.,… Fischman, A. J. (2006). Modafinil occupies dopamine and norepinephrine transporters in vivo and modulates the transporters and trace amine activity in vitro. *The Journal of Pharmacology and Experimental Therapeutics*, *319*(2), 561–569.

Marchant, N. L., Kamel, F., Echlin, K., Grice, J., Lewis, M., & Rusted, J. M. (2009). Modafinil improves rapid shifts of attention. *Psychopharmacology (Berl), 202,* 487–495.

McClellan, K. J., & Spencer, C. M. (1998). Modafinil. *CNS Drugs, 9*(4), 311–324.

Mereu, M., Bonci, A., Newman, A. H., & Tanda, G. (2013). The neurobiology of Modafinil as an enhancer of cognitive performance and a potential treatment for substance use disorders. *Psychopharmacology (Berl), 229*(3), 415–434.

Minzenberg, M. J., & Carter, C. S. (2008). Modafinil: A review of neurochemical actions and effects on cognition. *Neuropsychopharmacology, 33,* 1477–1502.

Moachon, G., Kanmacher, I., Clenet, M., & Matinier, D. (1996). Pharmacokinetic profile of Modafinil. *Drugs Today, 32,* 327–337.

Mohamed, A. D. (2014). The effects of Modafinil on convergent and divergent thinking of creativity: A randomized controlled trial. *Journal of Creative Behavior.* Available at: http://dx.doi.org/10.1002/jocb.1073 (Online ahead of publication)

Mohamed, A. D. (2015). The effects of Modafinil on motivation and salience of pleasure in healthy individuals: Quantitative evidence from the cognitive neurosciences. *AJOB Neuroscience, 6*(1), 15–17.

Müller, U., Rowe, J. B., Rittman, T., Lewis, C., Robbins, T. W., & Sahakian, B. K. (2013). Effects of Modafinil on non-verbal cognition, task enjoyment and creative thinking in healthy volunteers. *Neuropharmacology, 64,* 490–495.

Müller, U., Steffenhagen, N., Regenthal, R., & Bublak, P. (2004). Effects of Modafinil on working memory processes in humans. *Psychopharmacology (Berl), 177*(1–2), 161–169.

Pigeau, R., Naitoh, P., Buguet, A., McCann, C., Baranski, J., Taylor, M.,… & Mack, I. (1995). Modafinil, D-amphetamine and placebo during 64 hours of sustained mental work. I. Effects on mood, fatigue, cognitive performance and body temperature. *Journal of Sleep Research*, *4*(4), 212–228.

Randall, D. C., Shneerson, J. M., & File, S. E. (2005). Cognitive effects of Modafinil in student volunteers may depend on IQ. *Pharmacology, Biochemistry and Behavior, 82*(1), 133–139.

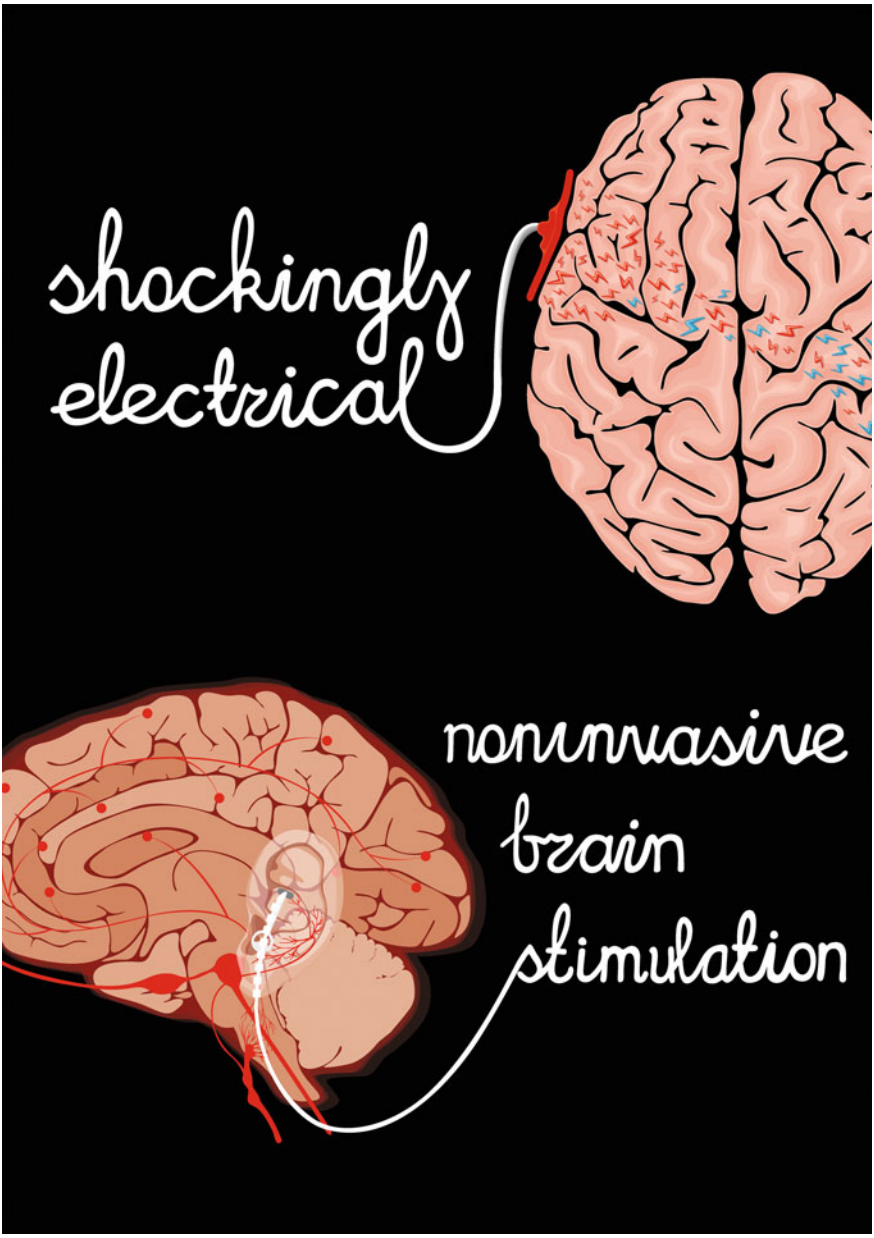
Stivalet, P., Esquivié, D., Barraud, P., Leifflen, D., & Raphel, C. (1998). Effects of Modafinil on attentional processes during 60 hours of sleep deprivation. *Human Psychopharmacology, 13*(7), 501–507.

Turner, D. C., Robbins, T. W., Clark, L., Aron, A. R., Dowson, J., & Sahakian, B. J. (2003). Cognitive enhancing effects of Modafinil in healthy volunteers. *Psychopharmacology (Berl), 165,* 260–269.

Whitmore, J., Doan, B., Fischer, J., French, J., & Heintz, T. (2004). *The efficacy of Modafinil as an operational fatigue countermeasure over several days of reduced sleep during a simulated*

escape and evasion scenario (No. AFRL-HE-BR-TR-2002–0021). Air force research lab brooks AFB TX human effectiveness DIR/biodynamics and protection DIV.

Whitmore, J., Hickey, P., Doan, B., Harrison, R., Kisner, J., Beltran, T.,… & Marks, F. (2006). *A double-blind placebo-controlled investigation of the efficacy of Modafinil for maintaining alertness and performance in sustained military ground operations*. AIR FORCE RESEARCH LAB BROOKS AFB TX HUMAN EFFECTIVENESS DIR/BIODYNAMICS AND PROTECTION DIV.


shockingly electrical
noninvasive brain stimulation

Part III
Shockingly Electrical—Noninvasive Brain Stimulation

Introduction

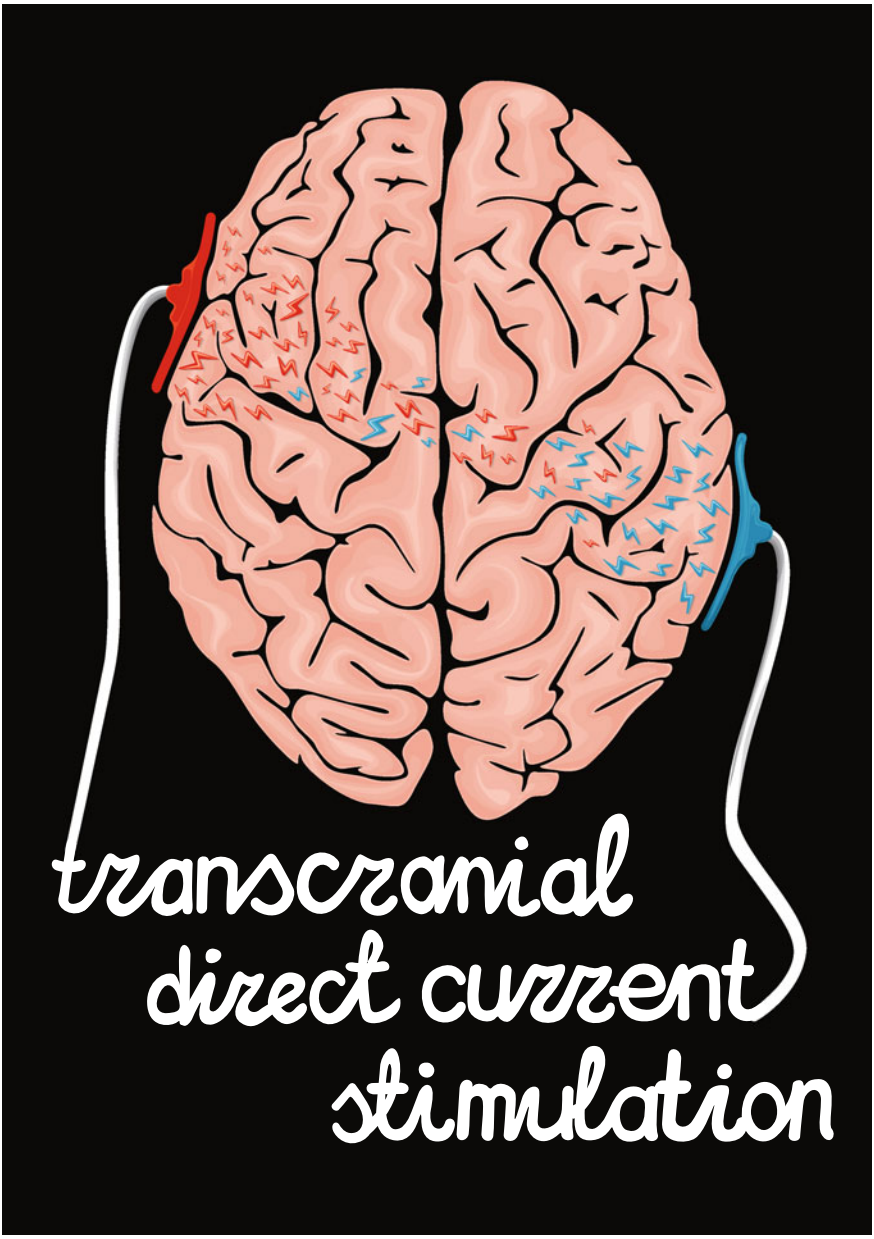
The present part aims to explore the strategy to enhance cognitive processes by means of noninvasive brain stimulation. The idea that we can influence neurons with electricity goes back to the late eighteenth century when Luigi Galvani found out that the muscles of dead frog legs twitched when hit by direct current on the nervous system. Earlier this century patients were, and still are, treated with electroconvulsive therapy as a treatment for severe depression (Fink 1984). Fortunately, new devices were recently invented that use electricity to influence neuronal activity in a less invasive way. This part is devoted to three of these techniques: transcranial direct current stimulation (tDCS), transcutaneous vagus nerve (tVNS), and trigeminal nerve stimulation (TNS). In contrast to imaging techniques, which are only correlational, by means of these techniques it is possible to infer a causal relation between the stimulated neurotransmitter/brain area and a related cognitive function.

It is crucial to keep in mind that, theoretically, such techniques act via different mechanisms of action. tDCS, which modifies brain excitability through weak, direct electric currents, is assumed to be a top-down technique—indirectly modulate subcortical activity through primary network changes in cortical activity (Shiozawa et al. 2014). In contrast, tVNS and TNS are bottom-up techniques—the propagation of the afferent signal from the vagus and trigeminal nerve travels from peripheral nerves toward the brain stem and from there to higher cortical structures. Accordingly, in Chapter "Transcranial Direct Current Stimulation" the evidence of the enhancing effect of tDCS on social cognition, via top-down mechanisms, is discussed. Further, in Chapter "Transcutaneous Vagus and Trigeminal Nerve Stimulation" how tVNS and TNS, via bottom-up mechanisms, may facilitate cognitive control and memory processes will be illustrated.

References

Fink, M. (1984). Meduna and the origins of convulsive therapy. *American Journal of Psychiatry, 141*(9), 1034–1041.

Shiozawa, P., Silva, M. E. D., Carvalho, T. C. D., Cordeiro, Q., Brunoni, A. R., & Fregni, F. (2014). Transcutaneous vagus and trigeminal nerve stimulation for neuropsychiatric disorders: A systematic review. *Arquivos de Neuro-psiquiatria, 72*(7), 542–547.


transcranial
direct current
stimulation

Transcranial Direct Current Stimulation

Roberta Sellaro, Michael A. Nitsche and Lorenza S. Colzato

Introduction

Over the last decades, we have witnessed an explosive advancement in noninvasive technologies for interacting in a safe and painless way with the brain and inducing direct and indirect changes in cortical excitability (George and Aston-Jones 2010; Fox 2011). Among these techniques, transcranial direct current stimulation (tDCS) (Nitsche and Paulus 2011) has become recognized as a promising tool in neuroscience research not only for understanding the relationship between brain and behavior but also as cognitive enhancer (Filmer et al. 2014). Similarly, to tACS, see Chapter "Transcranial Alternating Current Stimulation", tDCS is a "top-down" technique—that indirectly modulates subcortical activity through primary network changes in

R. Sellaro · L.S. Colzato (✉)
Cognitive Psychology Unit and Leiden Institute for Brain and Cognition, Leiden University, 2333 AK, Leiden, The Netherlands
e-mail: colzato@fsw.leidenuniv.nl

M.A. Nitsche
Department of Clinical Neurophysiology, Georg-August University Göttingen, 37075 Göttingen, Germany

M.A. Nitsche
Leibniz Research Centre for Working Environment and Human Resources, Dortmund, Germany

M.A. Nitsche
Department of Neurology, University Medical Hospital Bergmannsheil, Bochum, Germany

L.S. Colzato
Institute of Cognitive Neuroscience, Faculty of Psychology, Ruhr University Bochum, Bochum, Germany

L.S. Colzato, *Theory-Driven Approaches to Cognitive Enhancement*,
DOI 10.1007/978-3-319-57505-6_8

cortical activity. Several studies have provided converging evidence showing that tDCS is suited to modulate and enhance cognitive (Kuo and Nitsche 2012; 2015; Cohen-Kadosh 2015; Shin et al. 2015) and sensory-perceptual functioning (Costa et al. 2015). See also Chapter "The Application of Brain Stimulation and Neural Entrainment in Sport", if you are interested in the practical application of tDCS in enhancing motion perception and motor learning, crucial functions in sport science. However, by comparison, only a limited number of studies have investigated the enhancing effects of tDCS on socialcognition. Although the scarceness of research in this area, there is sufficient evidence to anticipate the potential of this technique to enhance social functioning and social decision-making.

In the present chapter, adapted from Sellaro et al. (2016), we intend to review the currently available findings stemming from recent studies that have successfully applied tDCS to enhance social behavior in healthy individuals. By providing this systematic overview, our goal is to help gain a better understanding of the potential of tDCS as a (social) cognitive enhancer. First, we will describe the mechanism of action of tDCS. Second, we will outline the recent available studies investigating the effect of tDCS on self-other representations. The studies point out that tDCS has promising potential for promoting social abilities. Last, we will identify potential modulators and individual differences in determining response to tDCS.

Mechanism of Action

In the classical protocols, tDCS delivers a low-intensity constant current, varying between 1 and 2 mA, via relatively large (25–35 cm^2) electrodes that are applied on the participants' scalp above brain regions of interest for a few minutes (5–20 min). At least two electrodes with opposite polarities, a positively charged anode and a negatively charged cathode, are needed, with the resulting current flowing from the anode toward the cathode (see Fig. 1). A limited but sufficient portion of the applied current enters the brain and is capable of altering spontaneous neural activity and excitability (Nitsche et al. 2008). During the last years, new protocols have been developed, which are assumed to deliver more focal effects, or network stimulation, by aid of smaller electrodes, or multi-electrode arrangements, often based on computational modeling (Nitsche et al. 2007; Edwards et al. 2013; Ruffini et al. 2014).

The current applied to the brain via tDCS is not of sufficient magnitude to generate action potentials (Nitsche et al. 2008). Rather, tDCS causes a sub-threshold modulation of the resting membrane potential of cortical neurons, altering their likelihood of firing, and thereby affecting spontaneous cortical activity (Bindman et al. 1964; Purpura and McMurtry 1965; Nitsche and Paulus 2000). The tDCS-induced shifts in the resting membrane potential are largely, although not entirely (see below) determined by the polarity of the stimulation. Anodal stimulation causes a slight depolarization of the resting membrane potential, which increases the probability of neural firing and, consequently, cortical excitability (Bindman et al. 1964; Purpura and McMurtry 1965; Nitsche and Paulus 2000).

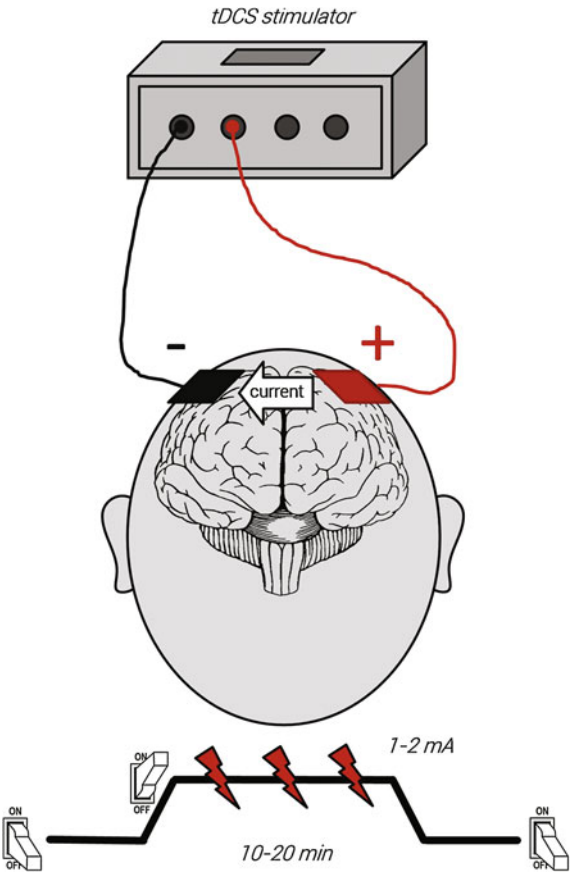


Fig. 1 During tDCS, a weak constant current (1–2 mA) is delivered to the brain via (at least) two electrodes with opposite polarities: a positively charged anode and a negatively charged cathode. Current is delivered for a few minutes (10–20 min) via a DC stimulator and it flows from the anode to the cathode

In contrast, cathodal stimulation leads to a slight hyperpolarization of the resting membrane potential, and hence to decreased probability of neural firing and excitability (Bindman et al. 1964; Purpura and McMurtry 1965; Nitsche and Paulus 2000). Changes in neural activity are observed during the stimulation period and, when the current is delivered for a sufficient period of time (i.e., at least 9–10 min), such changes can remain for longer than 1 h after the stimulation (Nitsche et al. 2008; Nitsche and Paulus 2000, 2001; Nitsche et al. 2003). This makes it possible to assess the cortical and behavioral effects of tDCS both during (online) and after (offline) the stimulation. Although online and offline tDCS-induced anodal and cathodal changes in cortical excitability are associated with similar neurophysiological effects, they seem to depend on different mechanisms (Stagg and Nitsche 2011). Broadly speaking, the primary effects of both anodal and cathodal tDCS during stimulation appear to solely depend on sub-threshold membrane polarization (Nitsche et al. 2003, 2005). Conversely, the aftereffects of tDCS seem to depend more on synaptic modulation, which is assumed to depend on strengthening (anodal tDCS) or weakening (cathodal tDCS) glutamatergic synapses, and reduction of

GABAergic activity independent from stimulation polarity (Nitsche et al. 2003, 2005; Stagg et al. 2009). However, activity of neuromodulators including dopamine, acetylcholine, and serotonin seems to play a role as well (Kuo et al. 2007; Monte-Silva et al. 2009; Nitsche et al. 2009, 2012).

The tDCS-induced changes in cortical excitability have been found to result in corresponding behavioral effects, whose direction is assumed to depend on the relation between the effects of stimulation polarity and task-dependent alterations of brain physiology (Shin et al. 2015; Nitsche et al. 2008). However, it is worth noting that all what we know about the physiological effects of tDCS, including the aforementioned link between tDCS-induced cortical and behavioral changes, comes primarily from studies that have focused on motor cortex excitability. Therefore, these principles do not necessarily apply one-to-one to stimulation of nonmotor areas, as the available evidence in fact suggests (Jacobson et al. 2012).

Besides the polarity of the stimulation, similarly to tACS (see Chapter "Transcranial Alternating Current Stimulation"), the tDCS-induced physiological and behavioral effects depend on a variety of other factors, such as electrode montage and size, current density, intensity and duration of the stimulation, but also state-dependency (i.e., the initial brain state) and inter-subject variability in terms of cortical anatomy, genetic polymorphisms, and psychological and motivational factors (Jacobson et al. 2012; Datta et al. 2012; Batsikadze et al. 2013; Tremblay et al. 2014; Li et al. 2015) (for further details, see Sect. "Factors affecting tDCS effects"). Among them, electrode montage is a crucial factor, and not just because it determines the polarity of the stimulation. As previously mentioned, tDCS needs at least two electrodes to work. Typically, one electrode (i.e., the target electrode) is placed over the brain area of interest and the other one (i.e., the return electrode) over another region (either cephalic or extracephalic). When both electrodes are placed on the scalp (i.e., bipolar cortical electrode montage) (Nasseri et al. 2015), one needs to keep in mind that not just the target electrode but also the return electrode will have a functional effect on the area where it is placed, thus introducing an important confounding factor when such a functional effect is not desired. To avoid that, researchers may opt for the use of an extracephalic electrode (i.e., monopolar extrachepahlic electrode montage), or for the use of a larger cephalic return electrode. Indeed, the use of a larger return electrode has been shown to be an effective and easy way to allow a functional monopolar montage because of smaller current density, when current strength is kept constant (Nitsche et al. 2007). Even in that case, however, the position of the return electrode will affect the physiological effects of tDCS, because it determines current flow direction through the brain. Current flow direction in relation to neuronal orientation is critical for the effects and direction of the effects of tDCS: for being effective, the electrical field has to meet the long axis of a neuron, and electrical field orientation in relation to neuronal orientation will determine excitability-enhancing or diminishing effects. This is the case because current has to enter and leave a given neuron to be effective. Because of higher receptor and ion channel density at the soma and axon hillock, it is assumed that current flow direction at these areas determines the effects of tDCS at the cellular level. In accordance, it was demonstrated that

dependent on neuronal orientation, tDCS of identical current flow direction has antagonistic effects in hippocampal slices (Kabakov et al. 2012), and that in the human brain, return electrode positions anterior and posterior to a target electrode result in different effects with identical target electrode stimulation polarity (Antal et al. 2004; Accornero et al. 2007).

Promoting Self-other Representations

In this section we describe recent studies that used tDCS to promote self–other representations.

By self–other representations we understand the ability to handle mental representations of both the self and other people—a fundamental ability for humans to engage in successful social interactions (Decety and Sommerville 2003; Spengler et al. 2009; Sowden and Shah 2014). Santiesteban et al. (2012) tested the role of the right temporoparietal junction (TPJ) in mediating the ability to distinguish and switch between concurrently activated self-related and other-related representations (i.e., self–other control) (Decety and Sommerville 2003; Spengler et al. 2009; Brass et al. 2009). In this study, anodal, cathodal, or sham tDCS was delivered over the right TPJ before participants executed three tasks, two of them requiring self-other control: a perspective-taking task (Keysar et al. 2000), which requires to inhibit one's own perspective and to enhance that of the other (Decety and Sommerville 2003), and a imitation-inhibition task (Brass et al. 2000), which instead requires to inhibit the other person's motor representations and to enhance the motor representations of one's own intended action (Spengler et al. 2009; Brass et al. 2009). The third task was a mental state attribution task (Lombardo et al. 2010) that did not require self–other representations to be controlled. Results showed that anodal tDCS, compared to cathodal and sham tDCS, improved online control of self–other representations in both perspective-taking and control-of-imitation tasks, without affecting performance in the mental state attribution task. These findings therefore corroborate the hypothesis that stimulating the right TPJ may promote self–other control over coactivated representations by inhibiting one's own or the other person's representations depending on the task demands (Decety and Sommerville 2003; Spengler et al. 2009; Brass et al. 2009; Ruby and Decety 2004). Interestingly, these results were replicated in a follow-up study in which Santiestaban et al. (2015) obtained evidence that the assumed role of the TPJ in self-other control is not restricted to the right TPJ but extends to the left TPJ as well. Indeed, they found that, compared to anodal stimulation of a control area, anodal TPJ stimulation improved self-other control in both perspective-taking and control-of-imitation tasks, regardless of whether the right or left TPJ was stimulated. Again, they did not observe any tDCS-induced effect on performance in a task tapping the ability to infer other's mental states. Further converging evidence supporting the role of the right TPJ in the control of imitation was provided by Hogeveen et al. (2015). In this study, following anodal tDCS of either the right TPJ or the right inferior frontal

cortex (IFC), or sham stimulation, participants were confronted with two critical tasks: a imitation-inhibition task (Brass et al. 2000), in which better performance requires to inhibit imitative behavior, and a social interaction task (Chartrand and Bargh 1999), in which higher mimicry levels signal better social interaction. Replicating the results observed by Santiesteban et al. (2012, 2015), right TPJ anodal tDCS, compared to sham, improved online control over imitative behavior, without affecting the degree of mimicry in the social interaction task. Instead, anodal tDCS of the right IFC, compared to sham tDCS, was found to have a dissociable effect on both tasks: similarly to anodal right TPJ tDCS, it improved the ability to inhibit imitation, but it also increased imitative behavior in the social interaction task. These results support the hypothesis that the right IFC, compared to the right TPJ, has a more direct impact on imitation, leading to either inhibit or enhance imitation, depending on task demands (Iacoboni et al. 1999; Heiser et al. 2003; Brass et al. 2005; Spengler et al. 2010; Sowden and Catmur 2015).

Taken together, these studies provide converging evidence for the critical role of the right TPJ in enhancing the online control of concurrently activated self-related and other-related representations. Interestingly enough, such a role for the right TPJ has recently been proven to mediate the ability to detect lies as well (Sowden et al. 2015). Indeed, using an offline protocol, Sowden et al. (2015) showed that anodal tDCS of the right TPJ, compared to anodal tDCS of a control area, improved lie-detection performance when participants were confronted with statements in which the to-be-judged opinions were in conflict with those held by the participants —a condition that in a previous experiment of the same study was found to significantly impair lie detection.

Other studies have provided evidence supporting the role of prefrontal cortex areas in promoting self-other representations. For instance, in another study the role of the anterior medial frontal cortex (AMFC) in self-other action discrimination was examined. Liepelt et al. (2016) delivered anodal, cathodal, or sham stimulation over either the AMFC or the right TPJ while participants performed a joint Simon task (Sebanz et al. 2003; Hommel et al. 2009; Dolk et al. 2013)—a turn-taking paradigm requiring the participant and a confederate to perform complementary parts of the same task. A more pronounced joint Simon effect (i.e., reduced self-other action discrimination) was found during excitability-reducing cathodal tDCS of the AMFC but not of the right TPJ—a finding that supports the assumed role of the AMFC in enhancing the representation of self-generated actions (Spengler et al. 2009; Brass et al. 2005, 2009). The absence of any tDCS effect during right TPJ stimulation instead further support the view that this area enhances online self-other control only when self-related and other-related representations are concurrently activated, as is the case in perspective-taking and control-of-imitation tasks (Decety and Sommerville 2003; Spengler et al. 2009; Brass et al. 2009; Ruby and Decety 2004). As such, these results are in line with the results observed by Santiesteban and colleagues (Santiesteban et al. 2012, 2015).

Finally, Sellaro et al. (2015) investigated the enhancing effect of tDCS over the medial prefrontal cortex (MPFC) in counteracting stereotypes activation resulting from in-group versus out-group categorization (Allport 1979; Greenwald and

Banaji 1995)—a situation in which self and other representations can be seen as polarized on a positive versus negative dimension. In this study, increased cognitive control over stereotypes activation with a resulting reduced implicit negative bias towards a social out-group was found in the group of participants who received online anodal tDCS of the MPFC, compared to participants who received cathodal or sham stimulation—a finding that speaks in favor of the idea that the stimulation of the MPFC may promote self-regulatory and cognitive-control processes implemented to overcome unwanted responses driven by stereotypes activation (Amodio and Frith 2006; Amodio et al. 2006). Interestingly, in the same sample of participants MPFC tDCS was not effective in enhancing interpersonal trust (Colzato et al. 2015), although MPFC activity has been linked to the degree of mutual trust (McCabe et al. 2001; Delgado et al. 2005; Krajbich et al. 2009).

Taken together, the studies reviewed in this section provide evidence supporting the role of tDCS over the TPJ and prefrontal cortex areas in enhancing several facets pertaining to the ability to handle self-other representations, and speak in favor of the possibility that the use of tDCS may represent a promising way to improve social abilities.

Factors Affecting tDCS Effects

In this section, we will consider the role of several factors that have been identified as playing a critical role in determining response to tDCS.

Like tACS, see Chapter "Transcranial Alternating Current Stimulation", several studies have shown that variations in stimulation parameters (e.g., intensity and duration of the stimulation, online versus offline stimulation, electrode size and number, scalp placement), can cause different amounts of electrical current to be delivered and, thus, can produce different tDCS effects. For instance, there is evidence that prolonged stimulation duration and higher current intensity can invert the polarity of the stimulation (Batsikadze et al. 2013). Likewise, in some occasions, online and offline tDCS have been found to produce differential, and even opposite effects (Stagg and Nitsche 2011; Pirulli et al. 2013). Also, although tDCS effects are not focal, electrode positioning is critical. Studies addressing tDCS-induced physiological changes and computational modeling studies of the expected current flow have found significant differences in the amount and distribution of current delivered to the brain depending on the relative positions of the electrodes (Minhas et al. 2012; Kessler et al. 2013; Woods et al. 2015). For instance, it has recently been shown that a drift of just 1 cm in electrode position causes a significant alteration of the distribution of the current flow and of the intensity of stimulation delivered to the brain (Woods et al. 2015). This is not surprising given that tDCS physiological and behavioral effects depend on the relation between current flow direction and neuronal orientation in the target area (Kabakov et al. 2012) and, thus, variations in electrode position are likely to alter such a relation. Importantly, this means that undesired drifts in electrode position during stimulation, due to a

superficial or an inappropriate placement of the electrodes, can seriously undermine reproducibility of the effects. Therefore, more efforts should be made in the attempt to create optimized procedures that can guarantee a stable placement of the electrodes on the scalp.

Computational models have suggested that individual anatomical differences can affect the current flow through the brain during the stimulation (Datta et al. 2012; Truong et al. 2013). Moreover, hair thickness may contribute to the observed variability in response to tDCS, as it may lead researchers to use a large amount of saline solution to saturate thicker hair (Horvath et al. 2014). Oversaturation of the electrode sponges can cause saline solution to spill over the sponges, with the consequence that the entire area of the scalp that is covered in saline will receive stimulation. Obviously, this can severely undermine reproducibility of tDCS application and effects. Also, tDCS effects have been found to depend on the baseline status of the brain, which can substantially vary across individuals (Antal et al. 2007; Benwell et al. 2015). Besides that, there is evidence that other factors such as age, gender, genetic polymorphisms, and psychological/motivational factors can influence the direction and the extent of the cortical and behavioral modulation (Krause and Cohen-Kadosh 2014). Therefore, to improve our understanding of whether and to what extent tDCS can enhance social behavior, it would be necessary for future studies to consider the role of interindividual differences. This implies testing sufficiently large samples to enable a deeper investigation of tDCS effects that can take into consideration and control for the role of interindividual variability. Moreover, computer modeling of the current flow through the brain can provide valuable information to be used to create optimal electrode montages for a given target area and head anatomy (Ruffini et al. 2013).

In sum, a detailed investigation of the factors that may influence tDCS-enhancing effects on social cognition in terms of both stimulation parameters and interindividual differences is highly advisable, especially given the recent controversy about the effectiveness of tDCS in modulating and enhancing cognitive processes (Horvath et al. 2015a, b).

Conclusion

Transcranial direct current stimulation has the potential to enhance social cognitive functioning by modulating brain excitability through weak, direct electric currents. tDCS seems to be sensitive to individual differences suggesting the necessity to take into account these differences in order to predict the enhancing response to tDCS. In particular, anodal tDCS over TPJ and prefrontal cortex areas seems to enhance the online control of concurrently activated self-related and other-related representations and to promote the ability to handle self-other representations. However, optimal protocols of stimulation (e.g., intensity and duration of the stimulation, online versus offline stimulation, electrode size and number, scalp placement) still need to be identified. Further, in order to find straightforward evidence that tDCS

improves social cognition, homogeneity across different studies, also in terms of study design and the specific task/questionnaire used, should be advisable. It is important to point out that extensive research is needed to confirm whether the observed tDCS enhanced social cognitive effects are maintained over time. While previous studies have shown that repetitive sessions of tDCS can intensify the effects of stimulation for memory, visual perception, and motor learning (Nitsche and Paulus 2011), it still needs to be explored whether the same applies to social cognitive functions. Although more research is needed to fully understand the effects tDCS exert on social cognition, we conclude that tDCS is a promising tool to improve social abilities.

References

Accornero, N., Voti, P. L., La Riccia, M., & Gregori, B. (2007). Visual evoked potentials modulation during direct current cortical polarization. *Experimental Brain Research, 178,* 261–266.

Allport, G. W. (1979). *The nature of prejudice*. Reading: Addison Wesley Publishing Company.

Amodio, D. M., & Frith, C. D. (2006). Meeting of minds: The medial frontal cortex and social cognition. *Nature Reviews Neuroscience, 7,* 268–277.

Amodio, D. M., Kubota, J. T., Harmon-Jones, E., & Devine, P. G. (2006). Alternative mechanisms for regulating racial responses according to internal vs external cues. *Social Cognitive and Affective Neuroscience, 1,* 26–36.

Antal, A., Kincses, T. Z., Nitsche, M. A., Bartfai, O., & Paulus, W. (2004). Excitability changes induced in the human primary visual cortex by transcranial direct current stimulation: Direct electrophysiological evidence. *Investigative Ophthalmology & Visual Science, 45,* 702–707.

Antal, A., Terney, D., Poreisz, C., & Paulus, W. (2007). Towards unravelling task-related modulations of neuroplastic changes induced in the human motor cortex. *European Journal of Neuroscience, 26,* 2687–2691.

Batsikadze, G., Moliadze, V., Paulus, W., Kuo, M. F., & Nitsche, M. A. (2013). Partially non-linear stimulation intensity-dependent effects of direct current stimulation on motor cortex excitability in humans. *The Journal of Physiology, 591,* 1987–2000.

Benwell, C. S., Learmonth, G., Miniussi, C., Harvey, M., & Thut, G. (2015). Non-linear effects of transcranial direct current stimulation as a function of individual baseline performance: Evidence from biparietal tDCS influence on lateralized attention bias. *Cortex, 69,* 152–165.

Bindman, L. J., Lippold, O. C. J., & Redfearn, J. W. T. (1964). The action of brief polarizing currents on the cerebral cortex of the rat during current flow and in the production of long-lasting after-effects. *The Journal of Physiology, 172,* 369–382.

Brass, M., Bekkering, H., Wohlschläger, A., & Prinz, W. (2000). Compatibility between observed and executed finger movements: Comparing symbolic, spatial, and imitative cues. *Brain and Cognition, 44,* 124–143.

Brass, M., Derrfuss, J., & von Cramon, D. Y. (2005). The inhibition of imitative and overlearned responses: A functional double dissociation. *Neuropsychologia, 43,* 89–98.

Brass, M., Ruby, P., & Spengler, S. (2009). Inhibition of imitative behaviour and social cognition. *Philosophical Transactions of the Royal Society of London B: Biological Sciences, 364,* 2359–2367.

Chartrand, T. L., & Bargh, J. A. (1999). The chameleon effect: The perception-behavior link and social interaction. *Journal of Personality and Social Psychology, 76,* 893–910.

Cohen Kadosh, R. (2015). Modulating and enhancing cognition using brain stimulation: Science and fiction. *Journal of Cognitive Psychology, 27,* 141–163.

Colzato, L. S., Sellaro, R., van den Wildenberg, W. P., & Hommel, B. (2015). tDCS of medial prefrontal cortex does not enhance interpersonal trust. *Journal of Psychophysiology, 29,* 131–134.

Costa, T. L., Lapenta, O. M., Boggio, P. S., & Ventura, D. F. (2015). Transcranial direct current stimulation as a tool in the study of sensory-perceptual processing. *Attention Perception and Psychophysics, 77,* 1813–1840.

Datta, A., Truong, D., Minhas, P., Parra, L. C., & Bikson, M. (2012). Inter-individual variation during transcranial direct current stimulation and normalization of dose using MRI-derived computational models. *Frontiers in Psychiatry, 3,* 91.

Decety, J., & Sommerville, J. A. (2003). Shared representations between self and other: A social cognitive neuroscience view. *Trends in Cognitive Sciences, 7,* 527–533.

Delgado, M. R., Frank, R. H., & Phelps, E. A. (2005). Perceptions of moral character modulate the neural systems of reward during the trust game. *Nature Neuroscience, 8,* 1611–1618.

Dolk, T., Hommel, B., Prinz, W., & Liepelt, R. (2013). The (not so) social Simon effect: A referential coding account. *Journal of Experimental Psychology. Human Perception and Performance, 39,* 1248–1260.

Edwards, D., Cortes, M., Datta, A., Minhas, P., Wassermann, E. M., & Bikson, M. (2013). Physiological and modeling evidence for focal transcranial electrical brain stimulation in humans: A basis for high-definition tDCS. *Neuroimage, 74,* 266–275.

Filmer, H. L., Dux, P. E., & Mattingley, J. B. (2014). Applications of transcranial direct current stimulation for understanding brain function. *Trends in Neurosciences, 37,* 742–753.

Fox, D. (2011). Brain buzz. *Nature, 472,* 156–159.

George, M. S., & Aston-Jones, G. (2010). Noninvasive techniques for probing neurocircuitry and treating illness: Vagus nerve stimulation (VNS), transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS). *Neuropsychopharmacology, 35,* 301–316.

Greenwald, A. G., & Banaji, M. R. (1995). Implicit social cognition: Attitudes, self-esteem, and stereotypes. *Psychological Review, 102,* 4e27.

Heiser, M., Iacoboni, M., Maeda, F., Marcus, J., & Mazziotta, J. C. (2003). The essential role of Broca's area in imitation. *European Journal of Neuroscience, 17,* 1123–1128.

Hogeveen, J., Obhi, S. S., Banissy, M. J., Santiesteban, I., Press, C., Catmur, C., et al. (2015). Task-dependent and distinct roles of the temporoparietal junction and inferior frontal cortex in the control of imitation. *Social Cognitive and Affective Neuroscience, 10,* 1003–1009.

Hommel, B., Colzato, L. S., & Van Den Wildenberg, W. P. (2009). How social are task representations? *Psychological Science, 20,* 794–798.

Horvath, J. C., Carter, O., & Forte, J. D. (2014). Transcranial direct current stimulation: Five important issues we aren't discussing (but probably should be). *Frontiers in Systems Neuroscience, 8,* 2.

Horvath, J. C., Forte, J. D., & Carter, O. (2015a). Evidence that transcranial direct current stimulation (tDCS) generates little-to-no reliable neurophysiologic effect beyond MEP amplitude modulation in healthy human subjects: A systematic review. *Neuropsychologia, 66,* 213–236.

Horvath, J. C., Forte, J. D., & Carter, O. (2015b). Quantitative review finds no evidence of cognitive effects in healthy populations from single-session transcranial direct current stimulation (tDCS). *Brain Stimulation, 8,* 535–550.

Iacoboni, M., Woods, R. P., Brass, M., Bekkering, H., Mazziotta, J. C., & Rizzolatti, G. (1999). Cortical mechanisms of human imitation. *Science, 286,* 2526–2528.

Jacobson, L., Koslowsky, M., & Lavidor, M. (2012). tDCS polarity effects in motor and cognitive domains: A meta-analytical review. *Experimental Brain Research, 216,* 1–10.

Kabakov, A. Y., Muller, P. A., Pascual-Leone, A., Jensen, F. E., & Rotenberg, A. (2012). Contribution of axonal orientation to pathway-dependent modulation of excitatory transmission by direct current stimulation in isolated rat hippocampus. *Journal of Neurophysiology, 107,* 1881–1889.

Kessler, S. K., Minhas, P., Woods, A. J., Rosen, A., Gorman, C., & Bikson, M. (2013). Dosage considerations for transcranial direct current stimulation in children: A computational modeling study. *PLoS ONE, 8,* e76112.

Keysar, B., Barr, D. J., Balin, J. A., & Brauner, J. S. (2000). Taking perspective in conversation: The role of mutual knowledge in comprehension. *Psychological Science, 11,* 32–38.

Krajbich, I., Adolphs, R., Tranel, D., Denburg, N. L., & Camerer, C. F. (2009). Economic games quantify diminished sense of guilt in patients with damage to the prefrontal cortex. *The Journal of Neuroscience, 29,* 2188–2192.

Krause, B., & Cohen Kadosh, R. (2014). Not all brains are created equal: The relevance of individual differences in responsiveness to transcranial electrical stimulation. *Frontiers in Systems Neuroscience, 8,* 25.

Kuo, M. F., Grosch, J., Fregni, F., Paulus, W., & Nitsche, M. A. (2007). Focusing effect of acetylcholine on neuroplasticity in the human motor cortex. *The Journal of Neuroscience, 27,* 14442–14447.

Kuo, M. F., & Nitsche, M. A. (2012). Effects of transcranial electrical stimulation on cognition. *Clinical EEG and Neuroscience, 43,* 192–199.

Kuo, M. F., & Nitsche, M. A. (2015). Exploring prefrontal cortex functions in healthy humans by transcranial electrical stimulation. *Neuroscience Bulletin, 31,* 198–206.

Li, L. M., Uehara, K., & Hanakawa, T. (2015). The contribution of interindividual factors to variability of response in transcranial direct current stimulation studies. *Frontiers in Cellular Neuroscience, 9,* 181.

Liepelt, R., Klempova, B., Dolk, T., Colzato, L. S., Ragert, P., Nitsche, M., et al. (2016). The medial frontal cortex mediates self-other discrimination in the Joint Simon task: A tDCS study. *Journal of Psychophysiology, 30,* 87–101.

Lombardo, M. V., Chakrabarti, B., Bullmore, E. T., Sadek, S. A., Pasco, G., Wheelwright, S. J. … & Daly, E. M. (2010). Atypical neural self-representation in autism. *Brain*, *133*, 611–624.

McCabe, K., Houser, D., Ryan, L., Smith, V., & Trouard, T. (2001). A functional imaging study of cooperation in two-person reciprocal exchange. *Proceedings of the National Academy of Sciences, 98,* 11832–11835.

Minhas, P., Bikson, M., Woods, A. J., Rosen, A. R., & Kessler, S. K. (2012). Transcranial direct current stimulation in pediatric brain: A computational modeling study. *Conference proceeding of the IEEE Engineering in Medicine and Biology Society, 2012,* 859–862.

Monte-Silva, K., Kuo, M. F., Thirugnanasambandam, N., Liebetanz, D., Paulus, W., & Nitsche, M. A. (2009). Dose-dependent inverted U-shaped effect of dopamine (D2-like) receptor activation on focal and nonfocal plasticity in humans. *The Journal of Neuroscience, 29,* 6124–6131.

Nasseri, P., Nitsche, M. A., & Ekhtiari, H. (2015). A framework for categorizing electrode montages in transcranial direct current stimulation. *Frontiers in Human Neuroscience, 9,* 54.

Nitsche, M. A., Cohen, L. G., Wassermann, E. M., Priori, A., Lang, N., Antal, A. … & Pascual-Leone, A. (2008). Transcranial direct current stimulation: State of the art 2008. *Brain Stimulation*, *1*, 206–223

Nitsche, M. A., Doemkes, S., Karakoese, T., Antal, A., Liebetanz, D., Lang, N. … & Paulus, W. (2007). Shaping the effects of transcranial direct current stimulation of the human motor cortex. *Journal of Neurophysiology*, *97*, 3109–3117

Nitsche, M. A., Fricke, K., Henschke, U., Schlitterlau, A., Liebetanz, D., Lang, N. … & Paulus, W. (2003). Pharmacological modulation of cortical excitability shifts induced by transcranial direct current stimulation in humans. *The Journal of Physiology*, 553, 293–301.

Nitsche, M. A., Kuo, M. F., Grosch, J., Bergner, C., Monte-Silva, K., & Paulus, W. (2009). D1-receptor impact on neuroplasticity in humans. *The Journal of Neuroscience, 29,* 2648–2653.

Nitsche, M. A., Müller-Dahlhaus, F., Paulus, W., & Ziemann, U. (2012). The pharmacology of neuroplasticity induced by non-invasive brain stimulation: Building models for the clinical use of CNS active drugs. *The Journal of Physiology, 590,* 4641–4662.

Nitsche, M. A., & Paulus, W. (2000). Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. *The Journal of Physiology, 527,* 633–639.

Nitsche, M. A., & Paulus, W. (2001). Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans. *Neurology, 57,* 1899–1901.

Nitsche, M. A., & Paulus, W. (2011). Transcranial direct current stimulation–update 2011. *Restorative Neurology and Neuroscience, 29,* 463–492.

Nitsche, M. A., Seeber, A., Frommann, K., Klein, C. C., Rochford, C., Nitsche, M. S. … & Paulus, W. (2005). Modulating parameters of excitability during and after transcranial direct current stimulation of the human motor cortex. *The Journal of Physiology*, *568*, 291–303.

Pirulli, C., Fertonani, A., & Miniussi, C. (2013). The role of timing in the induction of neuromodulation in perceptual learning by transcranial electric stimulation. *Brain Stimulation, 6,* 683–689.

Purpura, D. P., & McMurtry, J. G. (1965). Intracellular activities and evoked potential changes during polarization of motor cortex. *Journal of Neurophysiology, 28,* 166–185.

Ruby, P., & Decety, J. (2004). How would you feel versus how do you think she would feel? A neuroimaging study of perspective-taking with social emotions. *Journal of Cognitive Neuroscience, 16,* 988–999.

Ruffini, G., Fox, M. D., Ripolles, O., Miranda, P. C., & Pascual-Leone, A. (2014). Optimization of multifocal transcranial current stimulation for weighted cortical pattern targeting from realistic modeling of electric fields. *Neuroimage, 89,* 216–225.

Ruffini, G., Wendling, F., Merlet, I., Molaee-Ardekani, B., Mekonnen, A., Salvador, R. … & Miranda, P. C. (2013). Transcranial current brain stimulation (tCS): Models and technologies. *Neural Systems and Rehabilitation Engineering*, *21*, 333–345.

Santiesteban, I., Banissy, M. J., Catmur, C., & Bird, G. (2012). Enhancing social ability by stimulating right temporoparietal junction. *Current Biology, 22,* 2274–2277.

Santiesteban, I., Banissy, M. J., Catmur, C., & Bird, G. (2015). Functional lateralization of temporoparietal junction-imitation inhibition, visual perspective-taking and theory of mind. *European Journal of Neuroscience, 42,* 2527–2533.

Sebanz, N., Knoblich, G., & Prinz, W. (2003). Representing others' actions: Just like one's own? *Cognition, 88,* B11–B21.

Sellaro, R., Derks, B., Nitsche, M. A., Hommel, B., van den Wildenberg, W. P., van Dam, K., et al. (2015). Reducing prejudice through brain stimulation. *Brain Stimulation, 8,* 891–897.

Sellaro, R., Nitsche, M. A., & Colzato, L. S. (2016). The stimulated social brain: Effects of transcranial direct current stimulation on social cognition. *Annals of the New York Academy of Sciences, 1369*(1), 218–239.

Shin, Y. I., Foerster, Á., & Nitsche, M. A. (2015). Transcranial direct current stimulation (tDCS)–Application in neuropsychology. *Neuropsychologia, 74,* 74–95.

Sowden, S., & Catmur, C. (2015). The role of the right temporoparietal junction in the control of imitation. *Cerebral Cortex, 25,* 1107–1113.

Sowden, S., & Shah, P. (2014). Self-other control: A candidate mechanism for social cognitive function. *Frontiers in Human Neuroscience, 8,* 789.

Sowden, S., Wright, G. R., Banissy, M. J., Catmur, C., & Bird, G. (2015). Transcranial current stimulation of the temporoparietal junction improves lie detection. *Current Biology, 25,* 2447–2451.

Spengler, S., von Cramon, D. Y., & Brass, M. (2009). Control of shared representations relies on key processes involved in mental state attribution. *Human Brain Mapping, 30,* 3704–3718.

Spengler, S., von Cramon, D. Y., & Brass, M. (2010). Resisting motor mimicry: Control of imitation involves processes central to social cognition in patients with frontal and temporo-parietal lesions. *Social Neuroscience, 5,* 401–416.

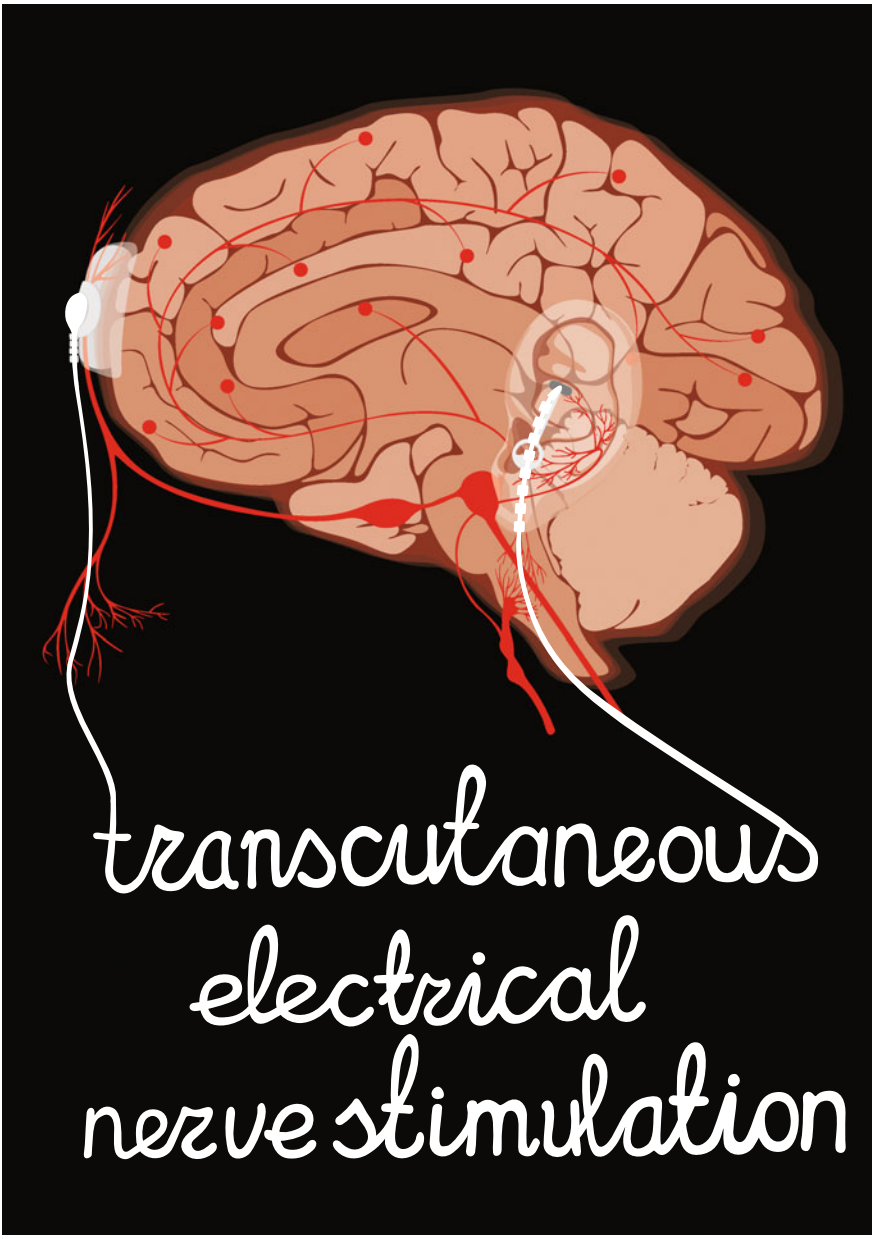
Stagg, C. J., Best, J. G., Stephenson, M. C., O'Shea, J., Wylezinska, M., Kincses, Z. T. … & Johansen-Berg, H. (2009). Polarity-sensitive modulation of cortical neurotransmitters by transcranial stimulation. *The Journal of Neuroscience*, *29*, 5202–5206.

Stagg, C. J., & Nitsche, M. A. (2011). Physiological basis of transcranial direct current stimulation. *The Neuroscientist, 17,* 37–53.

Tremblay, S., Lepage, J. F., Latulipe-Loiselle, A., Fregni, F., Pascual-Leone, A., & Théoret, H. (2014). The uncertain outcome of prefrontal tDCS. *Brain Stimulation, 7,* 773–783.

Truong, D. Q., Magerowski, G., Blackburn, G. L., Bikson, M., & Alonso-Alonso, M. (2013). Computational modeling of transcranial direct current stimulation (tDCS) in obesity: Impact of head fat and dose guidelines. *NeuroImage: Clinical*, *2*, 759–766.

Woods, A. J., Bryant, V., Sacchetti, D., Gervits, F., & Hamilton, R. (2015). Effects of electrode drift in transcranial direct current stimulation. *Brain Stimulation, 8,* 515–519.


transcutaneous
electrical
nerve stimulation

Transcutaneous Vagus and Trigeminal Nerve Stimulation

Lorenza S. Colzato and Kristl Vonck

Introduction

Recently, CE approved, noninvasive, transcutaneous (through the skin) vagus nerve (tVNS), and trigeminal nerve stimulation (TNS) devices have been developed. tVNS and TNS are noninvasive brain stimulation techniques that modulate brain activity via bottom-up mechanisms. That is, the stimulation of cranial nerves (with nuclei located in the brain stem) activates upstream monoaminergic nuclei and the cortex. As pointed out by Shiozawa et al. (2014) the vagus nerve innervates the nucleus tractus solitarious bilaterally, which is connected to the locus coeruleus (LC). Likewise, the trigeminal nerve is connected to brainstem nuclei that provide upstream pathways to the cortex. The trigeminal nerve has three major sensory branches over the face, all of which are bilateral. The trigeminal ganglion, positioned in the Meckel cave (cavum trigeminale), projects to the trigeminal nucleus, which owns bidirectional projections to the nucleus tractus solitarius, the LC, and the reticular formation. tVNS stimulates the afferent auricular branch of the vagus

L.S. Colzato (✉)
Cognitive Psychology Unit and Leiden Institute for Brain and Cognition, Leiden University, Leiden, The Netherlands
e-mail: colzato@fsw.leidenuniv.nl

K. Vonck
Laboratory for Clinical and Experimental Neurophysiology, Neurobiology and Neuropsychology, Department of Neurology, Ghent University Hospital, Ghent, Belgium
e-mail: colzato@fsw.leidenuniv.nl

L.S. Colzato
Institute of Cognitive Neuroscience, Faculty of Psychology, Ruhr University Bochum, Bochum, Germany

L.S. Colzato, *Theory-Driven Approaches to Cognitive Enhancement*,
DOI 10.1007/978-3-319-57505-6_9

nerve located medially of the tragus at the entry of the acoustic meatus (Kreuzer et al. 2012). In a seminal study, Fallgater et al. (2003) stimulated the tragus and were the first to demonstrate by means of early acoustic evoked potentials that real tVNS, compared to sham, produced a clear and reliable vagus sensory evoked potential in healthy participants. Further, it has been shown that the latencies of these evoked potential were longer in older than younger participants (Fallgatter et al. 2005). Keeping in mind that CE marked devices stimulate the concha of the ear but not the tragus, it would be crucial in future studies to replicate the findings by Fallgatter et al. (2003, 2005) in order to demonstrate that also the stimulation of the tragus is able to induce a solid and stable vagus sensory evoked potential.

tVNS, which was introduced for the first time by Ventureyra (2000), is safe and accompanied only by minor side effects, such as slight pain, burning, tingling, or itching sensation under the electrodes. A number of studies using high intensity tVNS have not found any major side effects (Dietrich et al. 2008; Kraus et al. 2007; Bauer et al. 2016). Given the right vagal nerve has efferent fibers to the heart, tVNS is safe to be performed only in the left ear (Kreuzer et al. 2012; Sperling et al. 2010). Following Kraus et al. (2007), a clever way to create a sham condition using tVNS is by attaching the stimulation electrodes to the center of the left ear lobe, which is partly innervated by the trigeminus but is known to be free of cutaneous vagal innervation (Peuker and Filler 2002), see Fig. 1. Indeed, two recent functional magnetic resonance imaging (fMRI) studies showed that this sham condition produced no activation in the cortex and brain stem (Kraus et al. 2013; Frangos et al. 2015). In contrast to tVNS, given that the trigeminal nerve has no efferent fibers to

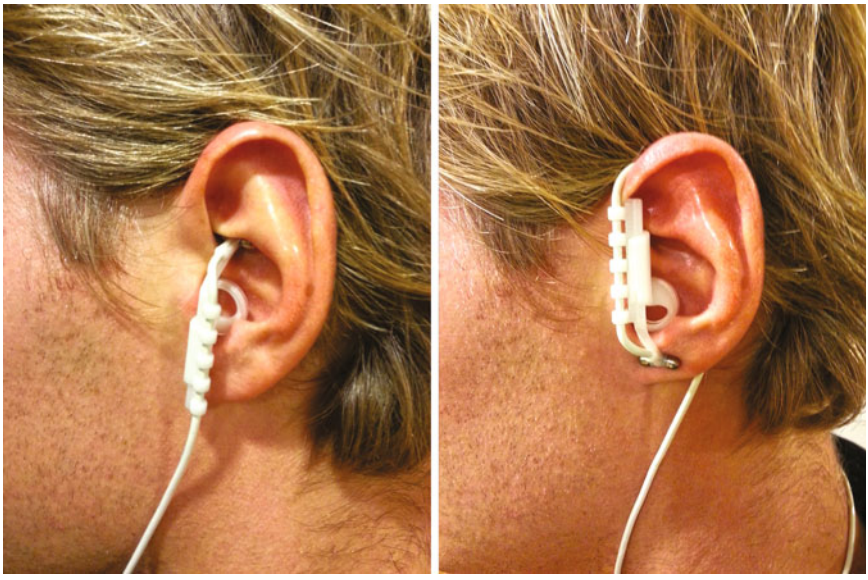


Fig. 1 Positioning of the stimulation electrodes in the active (*left*) and in the sham (*right*) condition

the heart, TNS can be applied bilaterally with potentially larger effects than unilateral stimulation (Fanselow et al. 2012; DeGiorgio et al. 2003). Like tVNS, TNS has been proven to be safe (Pop et al. 2011). Side effects are uncommon, temporary, and mild and include skin irritation, tingling, forehead pressure, and headache (Shiozawa et al. 2014). Two recent studies have shown that, compared to sham, TNS produced a clear and reliable change in the human blink reflex (Pilurzi et al. 2016; Mercante et al. 2015), thought to reflect brain stem plasticity (Aramideh and Ongerboer de Visser 2002; Cruccu and Deuschl 2000). These two studies have shown that TNS has direct modulatory effects at a subcortical level and are in line with the idea that TNS, like tVNS, works via "bottom-up" mechanisms (Shiozawa et al. 2014): the propagation of the afferent signal from the trigeminal nerve travels from peripheral nerves toward the brain stem and from there to intracranial subcortical and cortical structures.

So far, tVNS and TNS have been used to treat particular neuropsychiatric disorders such as major depression and epilepsy (Shiozawa et al. 2014) that are refractory to drugs. However, the focus of the present chapter is not on clinical populations but on healthy humans and how tVNS and TNS may be useful future tools to enhance cognition and mood. First, we will describe the mechanism of action of tVNS and TNS. Second, we will outline the available studies investigating the effect of tVNS on various cognitive processes related to the neurotransmitters targeted by the stimulation technique. Third, we will describe the available study investigating the effect of TNS on mood and various biochemical markers of stress response. The studies indicate that (a) tVNS and TNS have the potential to enhance cognitive functions, possibly following an inverted U-shaped relationship between stimulation intensity and cognitive performance; (b) TNS increases mood via reducing sympathetic activity in response to acute stress induction.

Mechanism of Action

We suggest that in healthy humans tVNS and TNS may exert their effect on cognition and mood via their modulatory action on monoaminergic nuclei by stimulating norepinephrine (NE) and gamma-aminobutyric acid (GABA) release, the two main neurotransmitters targeted directly by tVNS (van Leusden et al. 2015) and indirectly by TNS (Dieb and Hafidi 2015; DeGiorgio et al. 2011). In the paragraphs below, we will elaborate on the links between these noninvasive brain stimulation techniques and NE and GABA.

Link to NE

The afferent auricular branch of the vagus nerve ends in the nucleus of the solitary tract, which directly innervates the LC (Van Bockstaele et al. 1999)—the noradrenergic supply center of the brain (Aston-Jones et al. 1991). Given this

anatomical connection between the vagus nerve and the LC, it is reasonable to assume that VNS induces the release of NE by altering LC activity (George and Aston-Jones 2010). Consistent with that, there is evidence that acute VNS increases not only firing rates in the rat LC (Dorr and Debonnel 2006), but also the release of cortical and hippocampal NE (Hassert et al. 2004; Roosevelt et al. 2006; Follesa et al. 2007; Raedt et al. 2011). Moreover, two functional magnetic resonance imaging (MRI) studies in healthy humans have found that tVNS increased activation in the brainstem region including the LC and nucleus of the solitary tract, indicating that transcutaneous VNS is able to effectively stimulate vagal afferents to the brainstem (Dietrich et al. 2008; Frangos et al. 2015). In a similar way, trigeminal nuclei are connected to brainstem areas such as the nucleus tractus solitarii and the LC, which are thought to modulate the reticular formation (Aston-Jones et al. 1991). Similar to tVNS, TNS seems to increase the level of NE (Shiozawa et al. 2014). As a consequence of this increment of NE, very recently, given that one-third of the patients suffering from depression do not respond to pharmacological treatment, TNS has been proposed as a novel treatment for depression (Shiozawa et al. 2016).

Link to GABA

As pointed out by Vonck et al. (2014), so far, VNS has been mainly used to treat patients with epilepsy, who suffer from an abnormal reduction in GABA-ergic function (Treiman 2001). Not surprisingly, VNS has been found to successfully diminish the frequency and activity of seizures (DeGiorgio et al. 2000). A recent study by Capone et al. (2015), using the innovative approach of paired-pulse transcranial magnetic stimulation (TMS), suggests that tVNS acts by increasing GABA-ergic cortical activity. Indeed, short-interval intra-cortical inhibition, a double-pulse TMS paradigm index of GABA-A activity (Di Lazzaro et al. 2000), was significantly increased in the right motor cortex after real tVNS. The idea that tVNS does indeed enhance GABA levels is in line with the results of previous studies. VNS seems to increase the levels of free GABA in the cerebrospinal fluid (Ben-Menachem et al. 1995). Moreover, in epileptic patients receiving VNS for a year, GABA-A receptor density was significantly increased as compared to controls (Marrosu et al. 2003).

Along the same lines, so far, TNS has been primarily used to treat patients suffering from epilepsy. Despite the studies involving small sample sizes, TNS seems to significantly decrease mean seizure frequency and symptoms (DeGiorgi et al. 2006, 2009, 2013). Even though the neurophysiological mechanisms by which TNS modulates brain activity are still under debate, it seems plausible that TNS increases GABA levels and induces short- and long-lasting increases or decreases in synaptic transmission (Cooke and Bliss 2006; Bliss et al. 2014).

TVNS and NE and GABA-Related Functions: Post-Error Slowing, Memory and Multitasking

In this section, we will give an overview of recent findings involving the modulation of NE and GABA-related cognitive functions in healthy humans.

A phenomenon related to the LC-NE system is the so-called post-error slowing (PES): people tend to slow down their task performance after they make an error. Particularly, PES is indicated by longer reaction times (RTs) in trials following an error than in trials following a correct response (Rabbitt 1966). PES has been detected in an extensive range of tasks (Danielmeier and Ullsperger 2011), including the Stroop task (Gehring and Fencsik 2001), the flanker task (Debener et al. 2005; Krämer et al. 2007) and the Simon task (King et al. 2010; Danielmeier et al. 2011). Ullsperger et al. (2010) have suggested that slowing after negative feedback or unpredicted errors are connected to the activity of the neuromodulatory LC-NE system. Recently, Colzato et al. (2013) have demonstrated that an individual's magnitude of PES is predicted by the DBH5′-ins/del polymorphism—a variation in the DBH gene linked with the synthesis of the enzyme dopamine beta-hydroxylase, which is responsible for the conversion of dopamine into NE. Increased PES was associated with DBH5′-ins/del heterozygotes (linked to average level of plasma DβH activity) in contrast to del/del and ins/ins homozygous individuals (linked to low and high level of plasma DβH activity, respectively). Given, the correlational nature of genetic studies, causal evidence supporting the possible role of NE in mediating PES has been tested by the application of a single-session tVNS. A single-blind, sham-controlled, between-group design was used to assess the effect of tVNS in healthy young volunteers (n = 40) during two cognitive tasks designed to measure PES. Results showed increased PES during real tVNS, as compared to sham stimulation. This effect was of similar magnitude for the two tasks. These findings provide evidence for an important role of tVNS in facilitating PES (Sellaro et al. 2015).

Given that tVNS is believed to activate NE, which might facilitate neural plasticity by inducing long-term potentiation in the hippocampus (McIntyre et al. 2012; Sara 2009; Zuo et al. 2007), Jacobs and colleagues (2015) investigated the effect of a single-session tVNS on associative memory performance (as indexed by an associative face-name memory task) in healthy older individuals (n = 30). Real tVNS enhanced the number of hits in the memory task, compared to the sham condition. These outcomes support the role of tVNS as a promising neuromodulatory technique to improve associative memory performance in older individuals, even after a single session.

Another crucial cognitive function related to NE seems to be extinction memory. Indeed, memory consolidation seems to be facilitated in arousing conditions, when excitatory effects of peripheral epinephrine on the vagus nerve induce the release of NE in limbic brain structures (for a review, see Grimonprez et al. 2015). Accordingly, in a recent study, Burger et al. (2016) assessed whether tVNS can speed up extinction memory formation and retention in fear conditioned. In this study,

after fear conditioning, healthy humans (n = 31) were randomly assigned to get real tVNS or sham stimulation during the extinction phase. Retention of extinction memory was tested 24 h later. Real tVNS speeds up explicit fear extinction learning (US expectancy ratings), but did not induce better retention of extinction memory memory 24 h later.

tVNS stimulation seems not only to modulate NE-related but also GABA-related functions. Our daily life is characterized by multitasking situations, in which we are required to inhibit a planned, ongoing action and to rapidly adapt our behavior (e.g., to execute a different response). Successful performance under multitasking conditions relies on the ability to activate different task goals, and to cascade and prioritize different actions, which seems to rely on the GABA-ergic system. Indeed, a very recent magnetic resonance spectroscopy study showed that superior performance in action cascading was associated with increased concentrations of striatal GABA (Yildiz et al. 2014). Given, the correlational nature of MRS studies, it is, however, hard to infer the exact role of GABA in mediating action cascading. A recent study assessed the causal role of the GABA-ergic system in modulating the efficiency of action cascading by applying tVNS. A single-blind, sham-controlled, between-group design was used to assess the effect of real tVNS in healthy young volunteers (n = 30) on a stop-change paradigm. Results showed that real, as compared to sham stimulation, increased response selection functions during action cascading and led to faster responses when two actions are executed in succession (Steenbergen et al. 2015). These findings provide evidence for the crucial role of tVNS in enhancing performance in multitasking conditions.

Further, tVNS seems also to be a useful mean to examine conjoint effects of the GABA and NE system (Beste et al. 2016). Different lines of evidence suggest that the GABA-ergic and the noradrenergic system modulate inhibitory control processes. However, the concomitant increment in the GABAergic and NE system activity on inhibitory control needs still to be investigated. A single-blind, sham-controlled, between-group design was used to examine the effect of real tVNS in healthy young volunteers (n = 51) on two experimental paradigms indexing different aspect of inhibitory control; i.e., a backward inhibition paradigm and a response inhibition paradigm modulating working memory load (Beste et al. 2016). There were no effects of real tVNS on backward inhibition processes, but on response inhibition processes. Notably, these effects only appeared when working memory processes were needed to control response inhibition. Compared to sham stimulation, real tVNS produced better response inhibition performance (i.e., fewer false alarms).

Taken together, it seems that a single session of tVNS has the potential to enhance NE- and GABA-related cognitive functions. Particularly intriguing is the possibility to enhance certain memory functions across the life-span to compensate for cognitive decline in aging.

TNS, Biochemical Stress Response and Mood

In a recent study, composed of three experiments, Tyler et al. (2015) investigated the effect of TNS on biochemical stress response and mood in healthy participants. First, real TNS significantly suppressed basal sympathetic tone compared to sham as indicated by functional infrared thermography of facial temperatures. Second, after real TNS, compared to sham, participants reported significantly lower levels of tension and anxiety on the Profile of Mood States scale. Finally, when participants underwent a stress protocol, after real TNS, they showed a significant decrease in heart rate variability, galvanic skin conductance, and salivary α-amylase levels as compared to the sham condition. These preliminary results indicate that TNS increases mood via reducing sympathetic activity in response to acute stress induction.

TVNS and U-Shaped Function?

VNS seems to exhibit an inverted U-shaped relationship between stimulation intensity and memory performance. Indeed, Clark et al. (1995) showed that rats who received the intermediate stimulation of 0.4 mA current intensity showed significantly better avoidance memory than those in the 0.2, 0.8 mA or control condition. These results were also confirmed by a follow-up study from the same laboratory in humans suffering from epilepsy (Clark et al. 1999), showing that the intermediate stimulation intensity yielded the best performance in a recognition memory task. This is consistent with the inverted U-shaped Yerkes–Dodson principle (Yerkes and Dodson 1908) that, although originally advanced to explain performance decrements associated with too high or too low arousal levels with increasing task difficulty, seems to be suitable to account for several other nonlinear relationships (MacDonald et al. 2006). That being said, future studies should investigate whether tVNS and TNS and cognitive functions follow the same pattern of optimal performance at intermediate stimulation and cognitive decrements in case of too high or too low intensity stimulation.

Conclusion

tVNS and TNS have the potential to enhance cognition and mood via "bottom-up" mechanisms: the propagation of the afferent signal from the trigeminal nerve travels from peripheral nerves toward the brain stem and from there to higher subcortical and cortical structures. Even though comparison between studies is difficult since different devices were used by different research groups and the stimulation methods differ broadly, e.g., in intensity (mA) and frequency (Hz), it seems plausible that tVNS and TNS modulate cognition via NE and GABA, the two main

neurotransmitters stimulated by these techniques. The reviewed studies suggest that (a) tVNS and TNS have the potential to enhance cognitive functions, possibly following an inverted U-shaped relationship between stimulation intensity and cognitive performance; (b) TNS increases mood via reducing sympathetic activity in response to acute stress induction. Although more research is needed to fully understand the effects tVNS and TNS exert on cognition and mood at long term, we conclude that, at short term, tVNS and TNS are promising tools for enhancing cognitive functions.

References

Aramideh, M., & Ongerboer de Visser, B. W. (2002). Brainstem reflexes: Electrodiagnostic techniques, physiology, normative data, and clinical applications. *Muscle and Nerve, 26*(1), 14–30.

Aston-Jones, G., Shipley, M. T., Chouvet, G., Ennis, M., Van Bockstaele, E., Pieribone, V., et al. (1991). Afferent regulation of locus coeruleus neurons: Anatomy, physiology and pharmacology. *Progress in Brain Research, 88,* 47–75.

Bauer, S., Baier, H., Baumgartner, C., Bohlmann, K., Fauser, S., Graf, W., … & Mayer, T. (2016). Transcutaneous vagus nerve stimulation (tVNS) for treatment of drug-resistant epilepsy: A randomized, double-blind clinical trial (cMPsE02). *Brain Stimulation*, *9*(3), 356–363.

Ben-Menachem, E., Hamberger, A., Hedner, T., Hammond, E. J., Uthman, B. M., Slater, J., … & Wilder, B. J. (1995). Effects of vagus nerve stimulation on amino acids and other metabolites in the CSF of patients with partial seizures. *Epilepsy Research*, *20*(3), 221–227.

Beste, C., Steenbergen, L., Sellaro, R., Grigoriadou, S., Zhang, R., Chmielewski, W., Stock, A.-K., Colzato, L. (2016). Effects of concomitant stimulation of the GABAergic and norepinephrine system on inhibitory control—A study using transcutaneous vagus nerve stimulation. *Brain Stimulation, 9*(6), 811–818.

Bliss, T. V. P., Collingridge, G. L., & Morris, R. G. M. (2014). Synaptic plasticity in health and disease: Introduction and overview. *Philosophical Transactions of the Royal Society of London B: Biological Sciences, 369*(1633), 20130129.

Burger, A. M., Verkuil, B., Van Diest, I., Van der Does, W., Thayer, J. F., & Brosschot, J. F. (2016). The effects of transcutaneous vagus nerve stimulation on conditioned fear extinction in humans. *Neurobiology of Learning and Memory, 132,* 49–56.

Capone, F., Assenza, G., Di Pino, G., Musumeci, G., Ranieri, F., Florio, L., … & Di Lazzaro, V. (2015). The effect of transcutaneous vagus nerve stimulation on cortical excitability. *Journal of Neural Transmission*, *122*(5), 679–685.

Clark, K. B., Krahl, S. E., Smith, D. C., & Jensen, R. A. (1995). Post-training unilateral vagal stimulation enhances retention performance in the rat. *Neurobiology of Learning and Memory, 63*(3), 213–216.

Clark, K. B., Naritoku, D. K., Smith, D. C., Browning, R. A., & Jensen, R. A. (1999). Enhanced recognition memory following vagus nerve stimulation in human subjects. *Nature Neuroscience, 2*(1), 94–98.

Colzato, L. S., de Rover, M., van den Wildenberg, P. M., & Nieuwenhuis, S. (2013). Genetic marker of norepinephrine synthesis predicts individual differences in post-error slowing: A pilot study. *Neuropsychologia, 51,* 2600–2604.

Cooke, S. F., & Bliss, T. V. P. (2006). Plasticity in the human central nervous system. *Brain, 129* (7), 1659–1673.

Cruccu, G., & Deuschl, G. (2000). The clinical use of brainstem reflexes and hand-muscle reflexes. *Clinical Neurophysiology, 111*(3), 371–387.

Danielmeier, C., & Ullsperger, M. (2011). Post-error adjustments. *Frontiers in Psychology, 2,* 233.

Debener, S., Ullsperger, M., Siegel, M., Fiehler, K., Von Cramon, D. Y., & Engel, A. K. (2005). Trial-by-trial coupling of concurrent electroencephalogram and functional magnetic resonance imaging identifies the dynamics of performance monitoring. *Journal of Neuroscience, 25,* 11730–11737.

DeGiorgio, C. M., Fanselow, E. E., Schrader, L. M., & Cook, I. A. (2011). Trigeminal nerve stimulation: Seminal animal and human studies for epilepsy and depression. *Neurosurgery Clinics of North America, 22*(4), 449–456.

DeGiorgio, C. M., Murray, D., Markovic, D., & Whitehurst, T. (2009). Trigeminal nerve stimulation for epilepsy: Long-term feasibility and efficacy. *Neurology, 72*(10), 936–938.

DeGiorgio, C. M., Schachter, S. C., Handforth, A., Salinsky, M., Thompson, J., Uthman, B., … & Vaughn, B. (2000). Prospective long-term study of vagus nerve stimulation for the treatment of refractory seizures. *Epilepsia, 41(9)*, 1195–1200.

DeGiorgio, C. M., Shewmon, A., Murray, D., & Whitehurst, T. (2006). Pilot study of trigeminal nerve stimulation (TNS) for epilepsy: A proof-of-concept trial. *Epilepsia, 47*(7), 1213–1215.

DeGiorgio, C. M., Shewmon, D. A., & Whitehurst, T. (2003). Trigeminal nerve stimulation for epilepsy. *Neurology, 61*(3), 421–422.

DeGiorgio, C. M., Soss, J., Cook, I. A., Markovic, D., Gornbein, J., Murray, D., … & Heck, C. N. (2013). Randomized controlled trial of trigeminal nerve stimulation for drug-resistant epilepsy. *Neurology*, *80*(9), 786–791.

Di Lazzaro, V., Oliviero, A., Meglio, M., Cioni, B., Tamburrini, G., Tonali, P., et al. (2000). Direct demonstration of the effect of lorazepam on the excitability of the human motor cortex. *Clinical Neurophysiology, 111*(5), 794–799.

Dieb, W., & Hafidi, A. (2015). Mechanism of GABA involvement in post-traumatic trigeminal neuropathic pain: Activation of neuronal circuitry composed of PKCγ interneurons and pERK1/2 expressing neurons. *European Journal of Pain, 19*(1), 85–96.

Dietrich, S., Smith, J., Scherzinger, C., Hofmann-Preiß, K., Freitag, T., Eisenkolb, A., et al. (2008). A novel transcutaneous vagus nerve stimulation leads to brainstem and cerebral activations measured by functional MRI/Funktionelle Magnetresonanztomographie zeigt Aktivierungen des Hirnstamms und weiterer zerebraler Strukturen unter transkutaner Vagusnervstimulation. *Biomedizinische Technik/Biomedical Engineering, 53*(3), 104–111.

Dorr, A. E., & Debonnel, G. (2006). Effect of vagus nerve stimulation on serotonergic and noradrenergic transmission. *Journal of Pharmacology and Experimental Therapeutics, 318,* 890–898.

Fallgatter, A. J., Ehlis, A. C., Ringel, T. M., & Herrmann, M. J. (2005). Age effect on far field potentials from the brain stem after transcutaneous vagus nerve stimulation. *International Journal of Psychophysiology, 56*(1), 37–43.

Fallgatter, A. J., Neuhauser, B., Herrmann, M. J., Ehlis, A. C., Wagener, A., Scheuerpflug, P., … & Riederer, P. (2003). Far field potentials from the brain stem after transcutaneous vagus nerve stimulation. *Journal of Neural Transmission*, *110*(12), 1437–1443.

Fanselow, E. (2012). Central mechanisms of cranial nerve stimulation for epilepsy. *Surgical Neurology International, 3,* 247.

Follesa, P., Biggio, F., Gorini, G., Caria, S., Talani, G., Dazzi, L., … & Biggio, G. (2007). Vagus nerve stimulation increases norepinephrine concentration and the gene expression of BDNF and bFGF in the rat brain. *Brain Research*, *1179*, 28–34.

Frangos, E., Ellrich, J., & Komisaruk, B. R. (2015). Non-invasive access to the vagus nerve central projections via electrical stimulation of the external ear: fMRI evidence in humans. *Brain Stimulation, 8*(3), 624–636.

Gehring, W. J., & Fencsik, D. E. (2001). Functions of the medial frontal cortex in the processing of conflict and errors. *Journal of Neuroscience, 21,* 9430–9437.

George, M. S., & Aston-Jones, G. (2010). Noninvasive techniques for probing neurocircuitry and treating illness: Vagus nerve stimulation (VNS), transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS). *Neuropsychopharmacology, 35,* 301–316.

Grimonprez, A., Raedt, R., Baeken, C., Boon, P., & Vonck, K. (2015). The antidepressant mechanism of action of vagus nerve stimulation: Evidence from preclinical studies. *Neuroscience and Biobehavioral Reviews, 56,* 26–34.

Hassert, D. L., Miyashita, T., & Williams, C. L. (2004). The effects of peripheral vagal nerve stimulation at a memory-modulating intensity on norepinephrine output in the basolateral amygdala. *Behavioral Neuroscience, 118,* 79–88.

Jacobs, H. I., Riphagen, J. M., Razat, C. M., Wiese, S., & Sack, A. T. (2015). Transcutaneous vagus nerve stimulation boosts associative memory in older individuals. *Neurobiology of Aging, 36*(5), 1860–1867.

King, J. A., Korb, F. M., Von Cramon, D. Y., & Ullsperger, M. (2010). Post-error behavioral adjustments are facilitated by activation and suppression of task-relevant and task-irrelevant information processing. *Journal of Neuroscience, 30,* 12759–12769.

Krämer, U. M., Cunillera, T., Camara, E., Marco-Pallares, J., Cucurell, D., Nager, W., et al. (2007). The impact of catechol-*O*-methyltransferase and dopamine D4 receptor genotypes on neurophysiological markers of performance monitoring. *Journal of Neuroscience, 27,* 14190–14198.

Kraus, T., Hösl, K., Kiess, O., Schanze, A., Kornhuber, J., & Forster, C. (2007). BOLD fMRI deactivation of limbic and temporal brain structures and mood enhancing effect by transcutaneous vagus nerve stimulation. *Journal of Neural Transmission, 114*(11), 1485–1493.

Kraus, T., Kiess, O., Hösl, K., Terekhin, P., Kornhuber, J., & Forster, C. (2013). CNS BOLD fMRI effects of sham-controlled transcutaneous electrical nerve stimulation in the left outer auditory canal—A pilot study. *Brain Stimulation, 6*(5), 798–804.

Kreuzer, P. M., Landgrebe, M., Husser, O., Resch, M., Schecklmann, M., Geisreiter, F., et al. (2012). Transcutaneous vagus nerve stimulation: Retrospective assessment of cardiac safety in a pilot study. *Frontiers in Psychiatry, 3,* 70.

MacDonald, S. W., Nyberg, L., & Bäckman, L. (2006). Intra-individual variability in behavior: Links to brain structure, neurotransmission and neuronal activity. *Trends in Neurosciences, 29* (8), 474–480.

Marrosu, F., Serra, A., Maleci, A., Puligheddu, M., Biggio, G., & Piga, M. (2003). Correlation between GABA A receptor density and vagus nerve stimulation in individuals with drug-resistant partial epilepsy. *Epilepsy Research, 55*(1), 59–70.

McIntyre, C. K., McGaugh, J. L., & Williams, C. L. (2012). Interacting brain systems modulate memory consolidation. *Neuroscience and Biobehavioral Reviews, 36*(7), 1750–1762.

Mercante, B., Pilurzi, G., Ginatempo, F., Manca, A., Follesa, P., Tolu, E., et al. (2015). Trigeminal nerve stimulation modulates brainstem more than cortical excitability in healthy humans. *Experimental Brain Research, 233*(11), 3301–3311.

Peuker, E. T., & Filler, T. J. (2002). The nerve supply of the human auricle. *Clinical Anatomy, 15,* 35–37.

Pilurzi, G., Mercante, B., Ginatempo, F., Follesa, P., Tolu, E., & Deriu, F. (2016). Transcutaneous trigeminal nerve stimulation induces a long-term depression-like plasticity of the human blink reflex. *Experimental Brain Research, 234*(2), 453–461.

Pop, J., Murray, D., Markovic, D., & DeGiorgio, C. M. (2011). Acute and long-term safety of external trigeminal nerve stimulation for drug-resistant epilepsy. *Epilepsy & Behavior, 22*(3), 574–576.

Rabbitt, P. M. (1966). Errors and error correction in choice-response tasks. *Journal of Experimental Psychology, 71*(2), 264.

Raedt, R., Clinckers, R., Mollet, L., Vonck, K., El Tahry, R., Wyckhuys, T., … & Meurs, A. (2011). Increased hippocampal noradrenaline is a biomarker for efficacy of vagus nerve stimulation in a limbic seizure model. *Journal of Neurochemistry*, *117*, 461–469.

Roosevelt, R. W., Smith, D. C., Clough, R. W., Jensen, R. A., & Browning, R. A. (2006). Increased extracellular concentrations of norepinephrine in cortex and hippocampus following vagus nerve stimulation in the rat. *Brain Research, 1119,* 124–132.

Sara, S. J. (2009). The locus coeruleus and noradrenergic modulation of cognition. *Nature Reviews Neuroscience, 10*(3), 211–223.

Sellaro, R., van Leusden, J. W., Tona, K. D., Verkuil, B., Nieuwenhuis, S., & Colzato, L. S. (2015). Transcutaneous vagus nerve stimulation (tVNS) enhances post-error slowing. *Journal of Cognitive Neuroscience, 27,* 2126–2132.

Shiozawa, P., Silva, M. E. D., Carvalho, T. C. D., Cordeiro, Q., Brunoni, A. R., & Fregni, F. (2014). Transcutaneous vagus and trigeminal nerve stimulation for neuropsychiatric disorders: A systematic review. *Arquivos de Neuro-Psiquiatria, 72*(7), 542–547.

Shiozawa, P., Silveira, J. G., Soares, A., Taiar, I., Trevizol, A., Dias, Á. M., et al. (2016). Electroencephalographic changes following a trigeminal nerve stimulation (TNS) protocol: Assessing a novel depression treatment. *Epilepsy & Behavior, 58,* 141–142.

Sperling, W., Reulbach, U., Bleich, S., Padberg, F., Kornhuber, J., & Mueck-Weymann, M. (2010). Cardiac effects of vagus nerve stimulation in patients with major depression. *Pharmacopsychiatry, 43,* 7–11.

Steenbergen, L., Sellaro, R., Stock, A. K., Verkuil, B., Beste, C., & Colzato, L. S. (2015). Transcutaneous vagus nerve stimulation (tVNS) enhances response selection during action cascading processes. *European Neuropsychopharmacology, 25*(6), 773–778.

Treiman, D. M. (2001). GABAergic mechanisms in epilepsy. *Epilepsia, 42,* 8–12.

Tyler, W. J., Boasso, A. M., Mortimore, H. M., Silva, R. S., Charlesworth, J. D., Marlin, M. A., … & Pal, S. K. (2015). Transdermal neuromodulation of noradrenergic activity suppresses psychophysiological and biochemical stress responses in humans. *Scientific Reports*, *5*: 13865.

Ullsperger, M., Harsay, H. A., Wessel, J. R., & Ridderinkhof, K. R. (2010). Conscious perception of errors and its relation to the anterior insula. *Brain Structure and Function, 214*(5–6), 629–643.

Van Bockstaele, E. J., Peoples, J., & Telegan, P. (1999). Efferent projections of the nucleus of the solitary tract to peri-locus coeruleus dendrites in rat brain: Evidence for a monosynaptic pathway. *Journal of Comparative Neurology*, *412*(3), 410–428.

van Leusden, J. W., Sellaro, R., & Colzato, L. S. (2015). Transcutaneous Vagal Nerve Stimulation (tVNS): A new neuromodulation tool in healthy humans? *Frontiers in Psychology, 6,* 102.

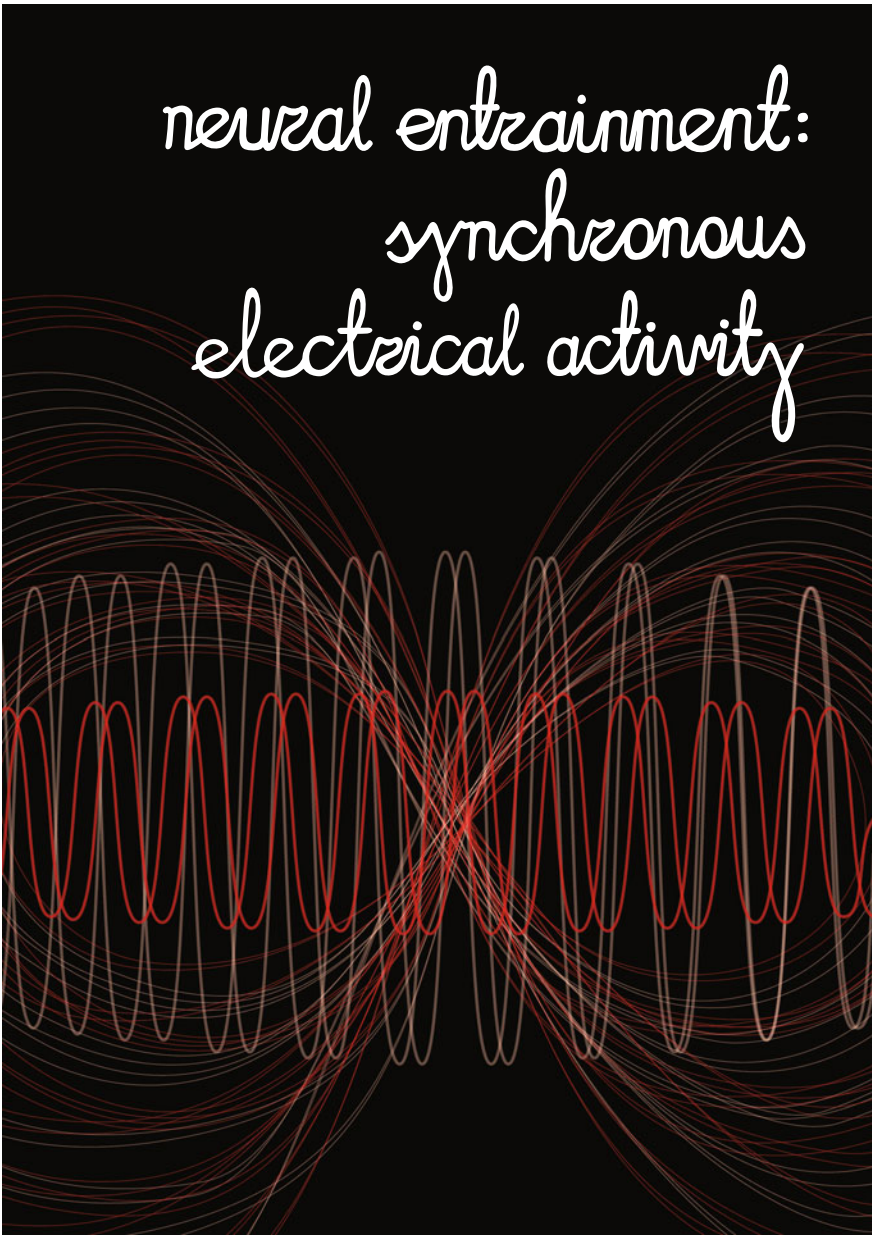
Ventureyra, E. C. (2000). Transcutaneous vagus nerve stimulation for partial onset seizure therapy. *Child's Nervous System, 16*(2), 101–102.

Vonck, K., Raedt, R., Naulaerts, J., De Vogelaere, F., Thiery, E., Van Roost, D., … & Boon, P. (2014). Vagus nerve stimulation… 25 years later! What do we know about the effects on cognition? *Neuroscience & Biobehavioral Reviews*, *45*, 63–71.

Yerkes, R. M., & Dodson, J. D. (1908). The relation of strength of stimulus to rapidity of habit-formation. *Journal of Comparative Neurology and Psychology, 18*(5), 459–482.

Yildiz, A., Quetscher, C., Dharmadhikari, S., Chmielewski, W., Glaubitz, B., Schmidt-Wilcke, T., … Beste, C. (2014). Feeling safe in the plane: Neural mechanisms underlying superior action control in airplane pilot trainees—a combined EEG/MRS study. *Human Brain Mapping. 35*, 5040–5051.

Zuo, Y., Smith, D. C., & Jensen, R. A. (2007). Vagus nerve stimulation potentiates hippocampal LTP in freely-moving rats. *Physiology & Behavior, 90*(4), 583–589.


neural entrainment:
synchronous
electrical activity

Part IV
Neural Entrainment—Synchronous Electrical Activity

Introduction

The present part aims to explore neural entrainment techniques by means of which the brain "takes over" or synchronizes its activity on the basis of external or internal stimulation. The theoretical idea behind neural entrainment is that the rhythmic oscillatory activity within and between different brain regions can enhance cognitive functioning.

Conceptually, noninvasive brain stimulation techniques (see Chapter "Transcranial Direct Current Stimulation"), such as transcranial direct current stimulation (tDCS), and neural entrainment techniques, such as neurofeedback, transcranial alternating current stimulation (tACS) and binaural beats, operate on different mechanisms of action. While tDCS modifies brain excitability through weak, direct electric currents, neurofeedback, tACS and binaural beats are techniques influencing the brain control on human action by modulation of brain oscillations (Paulus 2011).

Similar to tDCS, tACS protocols apply weak electrical current to the scalp through two or more electrodes placed over brain areas of interest. However, while tDCS is used to induce a constant current flow, tACS is used to apply an oscillatory (sinusoidal) electrical stimulation of a specific frequency to modulate neuronal membrane potentials in a frequency-dependent manner. Particularly, tACS is supposed to enhance cortical oscillations at frequencies close to the stimulation frequency and to entrain or synchronize neuronal networks (see Chapter "Transcranial Alternating Current Stimulation").

In contrast to tACS, neurofeedback training (see Chapter "Neurofeedback") provides individuals with real-time information about their level of cortical activity via sounds or visual displays, and with neurofeedback training, brain waves are recorded. An online spectrum analysis is implemented, which enables rewarding participants in order to lead them to increase or decrease the power in the targeted frequency band(s). By doing so, people are able to alter (enhance or reduce) the power of specific frequency bands in their own EEG signal (Huster et al. 2014).

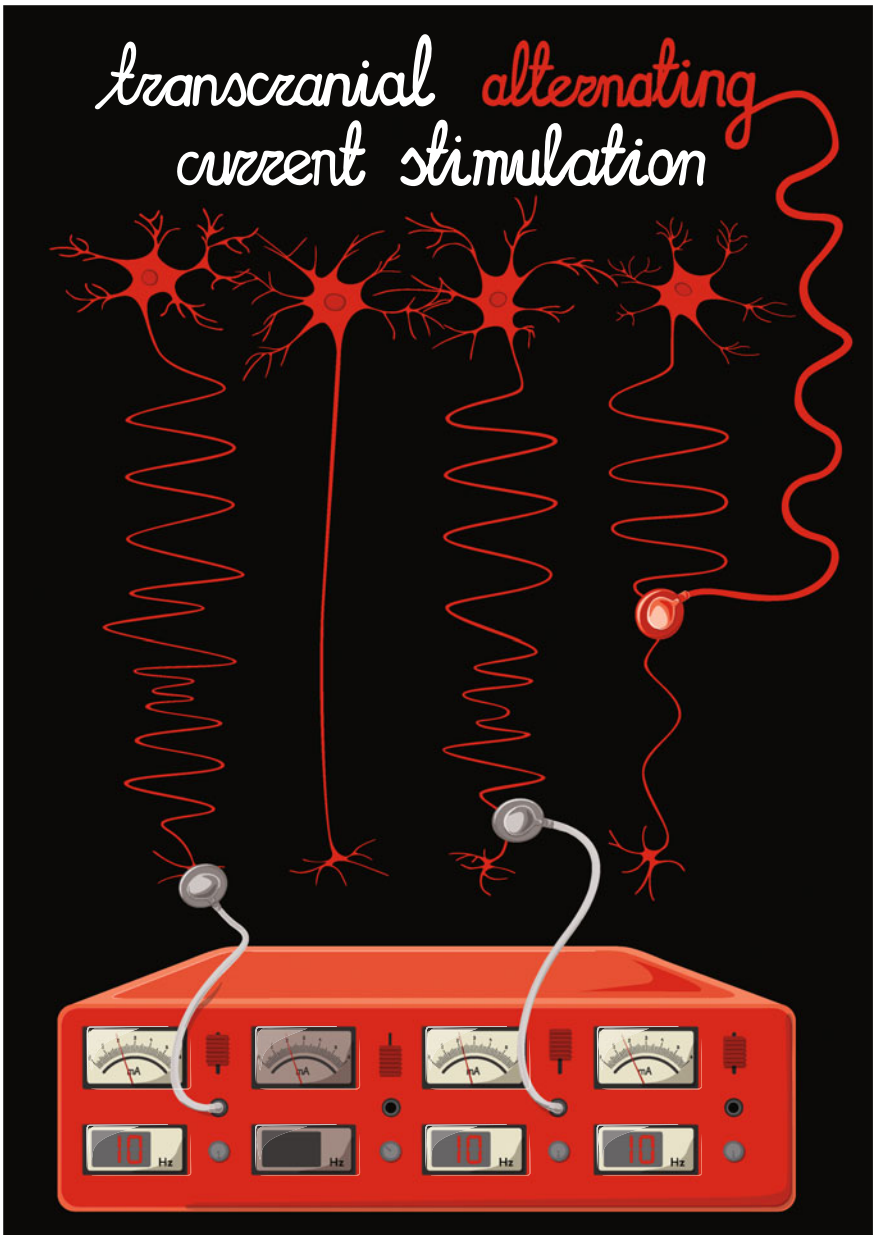
Similar to tACS, binaural beats may be used for brainwave entrainment as well. However, while tACS is used to apply an oscillatory (sinusoidal) electrical stimulation of a specific frequency, the entrainment via binaural beats is induced by presenting two beats of slightly different frequency (for instance 300 and 340 Hz) through headphones (see Chapter "Binaural Beat Stimulation"). As a result, the individual detects a single beat that differs in amplitude at a frequency equal to the difference between the two presented beats (40 Hz). The basic assumption is that listening to binaural beats in a specific frequency band will entrain the same frequency in the brain (Becher et al. 2015).

References

Becher, A. K., Höhne, M., Axmacher, N., Chaieb, L., Elger, C. E., & Fell, J. (2015). Intracranial electroencephalography power and phase synchronization changes during monaural and binaural beat stimulation. *European Journal of Neuroscience, 41*(2), 254–263.

Huster, R. J., Mokom, Z. N., Enriquez-Geppert, S., & Herrmann, C. S. (2014). Brain-computer interfaces for EEG neurofeedback: Peculiarities and solutions. *International Journal of Psychophysiology, 91*(1), 36–45.

Paulus, W. (2011). Transcranial electrical stimulation (tES—tDCS; tRNS; tACS) methods. *Neuropsychological Rehabilitation, 21*(5), 602–617.


transcranial alternating
current stimulation
mA
Hz
10

Transcranial Alternating Current Stimulation

Lorenza S. Colzato, Vera Mekern, Michael A. Nitsche and Roberta Sellaro

Introduction

An important attribute of neuronal activity are oscillations that can be measured by electroencephalography (EEG) or magnetoencephalography (MEG; Fröhlich 2014; Thut and Miniussi 2009). The rhythmic oscillatory activity within and between different brain regions is thought to be causally linked to higher order cognitive abilities, such as attention, perception, cognitive control, and memory (Herrmann et al. 2015; Thut and Miniussi 2009). Transcranial alternating current stimulation (tACS) is a neural entrainment technique which influences the brain control on human action by modulation of brain oscillations (Antal and Paulus 2013). Similarly, to tDCS, see Chapter "Transcranial Direct Current Stimulation", tACS is a

L.S. Colzato (✉) · V. Mekern · R. Sellaro
Cognitive Psychology Unit and Leiden Institute for Brain and Cognition, Leiden University, 2333 AK, Leiden, The Netherlands
e-mail: colzato@fsw.leidenuniv.nl

M.A. Nitsche
Department of Clinical Neurophysiology, Georg-August University Göttingen, 37075 Göttingen, Germany

M.A. Nitsche
Leibniz Research Centre for Working Environment and Human Resources, Dortmund, Germany

M.A. Nitsche
Department of Neurology, University Medical Hospital Bergmannsheil, Bochum, Germany

L.S. Colzato
Institute of Cognitive Neuroscience, Faculty of Psychology, Ruhr University Bochum, Bochum, Germany

L.S. Colzato, *Theory-Driven Approaches to Cognitive Enhancement*,
DOI 10.1007/978-3-319-57505-6_10

"top–down" technique—that indirectly modulates subcortical activity through primary network changes in cortical activity. This technique is relatively cheap, comparably easy to conduct, and offers a reliable sham stimulation condition. Even though tACS is only in its beginnings, several studies have already supported the effectiveness of this technique to modulate and enhance cognitive functioning in healthy humans (for recent reviews see, Herrmann et al. 2015; Kuo and Nitsche 2015; Cohen Kadosh 2015; Fröhlich et al. 2014; Krause and Cohen Kadosh 2014; Antal and Paulus 2013). Notwithstanding the promising results gathered in this growing literature, more research is still needed to improve our understanding of the effects of tACS and to optimize protocols for future studies.

In this chapter, we provide a summary of the enhancing effects of tACS research on cognitive functions in healthy individuals. The primary aim of this chapter is to complement previous reviews (Herrmann et al. 2015; Kuo and Nitsche 2015; Cohen Kadosh 2015; Fröhlich et al. 2014; Krause and Cohen Kadosh 2014; Antal and Paulus 2013) so as to gain a better understanding of the conditions under which tACS has been found to be effective in enhancing cognitive functioning. First, we will describe the mechanism of action of tACS. Second, we will outline the recent available studies investigating the effect of tACS on various cognitive processes. The studies point out that tACS has promising potential for promoting memory, visual perception, motor learning, and creativity. Last, we will identify potential modulators of response to tACS.

Mechanism of Action

Similarly to transcranial direct current stimulation (tDCS), see Chapter "Transcranial Direct Current Stimulation", tACS protocols allow to deliver a weak electrical current to the scalp through two or more electrodes placed over areas of interest (Nitsche et al. 2008; Ruffini et al. 2013; Antal and Paulus 2013). However, while tDCS is used to induce a constant current flow that causes polarity-dependent effects on cortical excitability via tonic subthreshold polarization of neuronal membrane potentials, tACS is used to apply an oscillatory (sinusoidal) electrical stimulation of a specific frequency that modulate neuronal membrane potentials in a frequency-dependent manner (Fig. 1; Nitsche et al. 2008; Ruffini et al. 2013; Antal and Paulus 2013).

tACS is typically applied with stimulation intensities and durations similar to tDCS, and at oscillation frequencies within the EEG frequency spectrum (usually between 1 and 100 Hz). When applied within the typical EEG frequency spectrum, tACS does not seem to induce neuroplasticity but rather its primary effect seems to entail the modulation of spontaneous ongoing cortical oscillations (Antal et al. 2008). Specifically, tACS is assumed to be able to enhance cortical oscillations at frequencies close to the stimulation frequency and to entrain or synchronize neuronal networks (Reato et al. 2010, 2013; Antal and Paulus 2013; Ali et al. 2013; Helfrich et al. 2014b). However, when tACS is applied outside the typical EEG

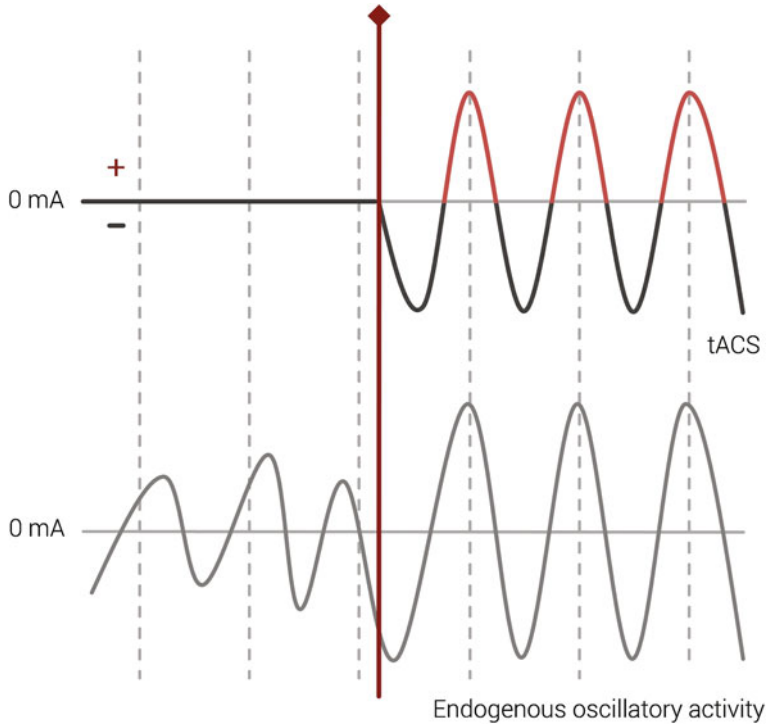


Fig. 1 In tACS two or more electrodes are used to apply an oscillatory (often sinusoidal) electrical current of a specific frequency to a targeted brain area. The *upper wave in the figure* shows how the sinusoidal wave oscillates around 0 mA. The applied current is hypothesized to entrain endogenous oscillatory activity to the frequency of the applied current, as shown in the *bottom part of the figure*. Therefore, endogenous activity becomes phase-locked with the applied current and gains power in the entrained frequency, as shown by higher amplitude

frequency range (e.g., at 140, 600 Hz, and in the low kHz range), tDCS-like neuroplastic excitability alterations are more likely to occur (Moliadze et al. 2010, 2012; Chaieb et al. 2011).

As tACS can interfere with naturally occurring cortical oscillations, this technique is suitable to probe the physiological and functional role of specific cortical oscillations in cognition, as the available findings indeed suggest (Herrmann et al. 2015; Kuo and Nitsche 2015; Cohen Kadosh 2015; Fröhlich et al. 2014; Krause and Cohen Kadosh 2014; Antal and Paulus 2013). Besides this, tACS can be used as an add-on tool to cognitive and/or motor training in order to optimize and enhance behavior.

However, more research is still needed to gain a better understanding of the physiological mechanisms of tACS and of the full potentialities of this technique. Online measurement of tACS effects via EEG or MEG monitoring is difficult due to artifacts induced by the stimulation. However, recent attempts aimed at separating neuronal activity from stimulation-induced artifacts corroborate the assumption of

entrainment (Neuling et al. 2015; Helfrich et al. 2014b). In addition, a recent in vitro study has simulated in vivo-like 'endogenous' oscillations in a mouse cortical slice and showed that application of an oscillating electrical field enhanced these endogenous oscillations (Schmidt et al. 2014). This again provides evidence for entrainment, which may extend to tACS applied to the human brain (Schmidt et al. 2014).

Enhancing Effects in Working Memory, Visual Processing, Motor Learning, and Creativity

Previous studies on tACS have effectively used this technique to enhance a wide range of functions, including working memory (WM; Jaušovec and Jaušovec 2014; Jaušovec et al. 2014; Meiron and Lavidor 2014; Polanía et al. 2012) and visual processing (Helfrich et al. 2014b; Laczó et al. 2012). In terms of cognitive enhancement, WM is particularly important in order to counteract the effects of healthy aging. First, in a seminal study it has been shown that tACS-induced theta-synchronized activity between left posterior parietal cortex and dorsolateral prefrontal cortex improved visual memory-matching reaction times. In contrast, tACS-induced frontoparietal theta phase desynchronization deteriorated performance (Polanía et al. 2012). Second, active tACS with individually determined theta frequency applied to the left parietal (target electrode = P3) but not to the frontal (target electrode = F3) brain areas significantly increased WM storage capacity (Jaušovec and Jaušovec 2014). Further, in a similar study, besides stimulating left frontal and left parietal, the authors stimulated also the right parietal areas and the enhancing effect of theta tACS on WM executive processes was most pronounced for right parietal stimulation (Jaušovec et al. 2014). Moreover, Meiron and Lavador (2014) showed that theta tACS improved online WM accuracy when the bilateral dorsolateral prefrontal cortex was actively stimulated compared to sham stimulation. Finally, very recently, Vosskuhl et al. (2015) tested the assumed causal role of the gamma/theta ratio in sustaining higher order cognitive functions, such as WM and short-term memory (Lisman and Jensen 2013; Roux and Uhlhaas 2014). To this end, they applied tACS over the frontal cortex to increase the gamma/theta ratio while engaging the participant in two tasks: one tapping WM performance (i.e., the backward digit span task), and one short-term memory performance (i.e., the forward digit span task). Gamma/theta ratio was increased by reducing the theta frequency that showed best phase-amplitude coupling to a gamma-range frequency, such that one extra gamma cycle fit onto the theta cycle. Improved short term, but not WM performance was observed during tACS, which increased gamma/theta ratio—however, the effect vanished after tACS offset. In contrast, WM performance might depend on theta synchronization between frontal and parietal areas instead, as suggested by earlier research (Polanía et al. 2012).

In sum, all the studies described above point out to a crucial role of theta band activity for enhancing WM.

In terms of visual perception, 10 Hz tACS applied over the parieto-occipital cortex has been shown to increase parieto-occipital alpha activity and to synchronize cortical oscillators with similar intrinsic frequencies to the entrainment frequency. Most importantly, tACS was effective in enhancing target detection performance in a phase-dependent fashion underlying, therefore, the causal role of alpha oscillations for visual perception. Related to that, a recent study aimed to assess how tACS affects motion perception in healthy humans (Kar and Krekelberg 2014). 10 Hz tACS of the left human middle temporal/V5 complex (hMT/V5 +) improved visual motion direction discrimination performance and attenuated motion adaptation of visual stimuli presented in the contralateral hemifield. Importantly, tACS was effective only when applied during the adaptation induction phase (i.e., when the adapter was on the screen), but not when applied before visual stimuli were presented or during recovery from motion adaptation (i.e., when the screen was blank). Given that prolonged stimulus presentations (i.e., adaptation) typically cause a reduction in motion discrimination performance (Van Wezel and Britten 2002), it is reasonable to speculate that tACS may have counteracted such a reduction, thereby leading to increased sensitivity. Therefore, these findings can be taken to suggest that tACS can attenuate motion adaptation. Further, Cecere et al. (2015) used tACS to probe the role of occipital cortical oscillations in audio–visual integration, as indexed by the sound-induced double-flash illusion. In this illusion, the presentation of two beeps within about 100 ms together with one flash elicits the perceptual illusion of a second flash (Shams et al. 2000). Given that alpha-band oscillations are known to cycle every $\sim$100 ms, tACS was delivered over the occipital cortex at either the individual alpha frequency (IAF)—previously estimated via task-concomitant EEG recording—or off-peak alpha frequencies (IAF $\pm$ 2 Hz). Results showed that compared to tACS at the IAF, tACS at slower (IAF $-$ 2 Hz) and faster (IAF + 2 Hz) frequencies increased and decreased the temporal window of the illusion, respectively. These findings suggest that occipital alpha oscillations may represent the neurophysiological substrate enabling audio–visual interactions.

Beyond alpha, also gamma band activity plays an important role in visual perception. In another study, pertaining to illusory perception, Cabral-Calderin et al. (2015) investigated the differential role of alpha (10-Hz) and gamma (60- and 80-Hz) frequencies in the resolution of perceptual ambiguity. Participants performed a bistable perception task while the occipital cortex was stimulated via tACS to increase cortical oscillations in the tested frequencies. Results showed that 60-Hz tACS increased spontaneous perceptual reversal rates, while no effects were observed for alpha (10 Hz) and higher gamma (80 Hz) frequencies—this suggests that gamma but not alpha oscillations are causally involved in the resolution of perceptual ambiguity of bistable stimuli.

The number of tACS studies investigating possible enhancing cognitive processes apart from perception and WM is still relatively small, but the available findings are promising. Especially, interesting from a cognitive enhancement perspective are studies published very recently showing that tACS is effective in modulating motor learning and creativity. First, Pollok et al. (2015) tested the role of motor-cortical

alpha and beta oscillations in motor sequence learning. tACS was applied over the left primary motor cortex while participants performed a serial reaction time task. Results showed that, compared to sham stimulation and tACS delivered at a control frequency of 35 Hz, both 10 Hz (alpha) and 20 Hz (beta) tACS facilitated the acquisition of a new motor sequence. Only 20 Hz tACS was found to stabilize the newly learned motor sequences immediately after acquisition. These findings partly replicate previous results reported by Antal et al. (2008) who observed implicit motor learning facilitation during 10-Hz tACS. Besides that, these results corroborate the hypothesis that motor-cortical beta oscillations may sustain and enhance motor control. See Chapter "The Application of Brain Stimulation and Neural Entrainment in Sport", for practical application of these results in sport science.

Second, Lustenberger et al. (2015) employed tACS to probe the causal role of prefrontal cortex alpha-band frequency activity (8–12 Hz) in divergent thinking—a style of creative thinking that allows the generation of innovative ideas. Results showed that 10-Hz, but not 40-Hz tACS delivered bilaterally over the dorsolateral prefrontal cortex during the execution of the Torrance Test of Creative Thinking (Baer 1993; Kim 2006) significantly improved task performance, compared to sham stimulation. This finding represents direct evidence for a causal role of prefrontal alpha oscillations in creative thinking, which is consistent with the conclusion of previous correlational studies (Fink et al. 2007; Fink and Benedek 2014; Jauk et al. 2012).

In sum, a growing body of evidence shows that tACS might enhance cognitive functioning by modulating rhythmic cortical activity within and between cortical areas. Specifically, theta tACS seems to support WM performance, whereas beta tACS sustains motor learning, and alpha and gamma tACS are more related to visual perception and creativity. Nonetheless, a full understanding of the factors influencing effects of this technique is still lacking (Battleday et al. 2014; Krause and Cohen Kadosh 2014). In the next section, we will provide a brief recap of the factors that can affect the tACS-induced effects on cognitive functioning.

Factors Affecting TACS Effects

Like tDCS, see Chapter "Transcranial Direct Current Stimulation", tACS-induced physiological and behavioral effects are likely to depend on a large number of factors, such as for example electrode montage, stimulation frequency, and duration of the stimulation (Krause and Cohen Kadosh 2014). These factors need to be considered in order to reach the optimal enhancing effect of the desired cognitive functions. Methodological studies may augment our knowledge about these factors considerably. For instance, computational modeling approaches can help to shed light about the optimal combination of stimulation parameters, and can offer important insight into the effects of different electrode montages (Iacono et al. 2015; Neuling et al. 2012; Paulus 2011), although more research is still needed to optimize and physiologically validate these models. Moreover, combining tACS with EEG and/or MEG measurements can further elucidate the mechanisms of action of tACS.

Electrode Montage

Likewise tDCS, tACS needs at least two electrodes to work: a target electrode, which is placed over the brain area of interest, and a reference or return electrode, which is positioned over another region (either cephalic or extracephalic). When the return electrode is placed on the scalp, it is typically positioned over a cortical region that is believed not to play any functional role in the experimental paradigm (Ruffini et al. 2014), and/or in some occasions its size is enlarged to make the area beneath the return electrode functionally inert (Nitsche et al. 2007). Current density modeling studies, however, have suggested that the position of the return electrode is critical in determining the electrical field distribution across the cortex as well as the electrical field distribution under the target electrode (Bikson et al. 2010). Therefore, as the effects of tACS result from the electrical polarization of neurons that are aligned with the applied field (Radman et al. 2009), the position of the return electrode is likely to be of critical importance. Empirical evidence supporting the critical role of the position of the return electrode comes from a recent study by Mehta et al. (2015). In this study, the left primary motor cortex was stimulated while varying the position of return electrode between four locations, two cephalic (fronto-orbital and contralateral primary motor cortex) and two extracephalic (ipsilateral and contralateral shoulder). Results confirmed that tACS-induced behavioral effects are critically dependent on the position of the return electrode, as only the montage with extracephalic return electrode contralateral to the target electrode was found to be effective in entraining physiological tremor.

Stimulation Frequency

Undoubtedly, stimulation frequency is a factor playing a crucial role in mediating tACS effects. It is often assumed that tACS entrains endogenous oscillations to the stimulation frequency (Battleday et al. 2014; Helfrich et al. 2014a). An already earlier mentioned in vitro study showed that tACS enhances endogenous oscillatory activity only when the applied stimulation matched the endogenous frequency (Schmidt et al. 2014). Moreover, whenever the cortical slice did not have an endogenous frequency, neuronal activity entrained to all tACS frequencies. This indicates that the endogenous oscillations constrain the effect of tACS to frequencies that match them. To effectively target neuronal oscillatory activity, the stimulation frequency should thus be adapted to the frequency that matches spontaneous dominant EEG activity and that it is assumed to correlate with the specific cognitive function of interest—an assumption that has received empirical support from several recent studies (Kanai et al. 2008; Voss et al. 2014; Lustenberger et al. 2015; Cabral-Calderin et al. 2015; Janik et al. 2015; Schaal et al. 2015). Importantly, as endogenous cortical rhythms vary interindividually (e.g., Pollock et al. 1991; Stassen et al. 1987), it is reasonable to assume that tACS may be more effective when applied at the individual endogenous frequency—again, an assumption that has received considerable support (e.g., Cecere et al. 2015).

This makes it necessary to assess individual endogenous frequency via EEG or MEG measurements, to tailor tACS frequency to the individual needs.

Stimulation Duration

The duration of the stimulation instead seems to be critically related to the likelihood of observing tACS after-effects. For instance, Strüber et al. (2015) tested the relationship between stimulation duration and the likelihood to observe tACS after-effects. They showed that alpha tACS applied intermittently for 1 s duration did not elicit any after-effects on EEG amplitude and phase, which were instead observed in a previous study with identical parameters in terms of intensity and electrode montage, but longer (i.e., 20 min) stimulation duration (Neuling et al. 2013). These results confirmed that stimulation duration is a critical factor for eliciting tACS after-effects, and can explain why no tACS after-effects have been observed in animal studies so far, which typically use stimulation protocols in the range of seconds (for a review, see Reato et al. 2013). More importantly, these results corroborate the hypothesis that tACS after-effects are due to changes in synaptic plasticity, which are unlikely to occur with too short stimulation durations. Consistent evidence supporting the notion that tACS after-effects reflect plastic changes rather than entrainment comes from another recent study by Vossen et al. (2015). The authors applied repeated tACS at individual alpha frequency. Stimulation intervals were manipulated, so that the follow-up stimulation was either in phase (continuous condition) or out of phase (discontinuous condition) in relation to the previous stimulation. After-effects (i.e., enhanced EEG alpha amplitude) were found regardless of the continuous versus discontinuous condition. This challenges the assumption that after-effects are due to entrainment, based on which only the continuous condition should have produced after-effects. Moreover, consistent with the results of Strüber et al. (2015), tACS after-effects were observed only for intermittent protocols of 8 s stimulation duration, but not for the shorter (i.e., 3 s) stimulation duration. Taken together, the findings of Strüber et al. (2015) and Vossen et al. (2015) support the idea that synaptic plasticity and not entrainment is the key factor responsible for tACS after-effects. However, more research is needed to confirm that such short stimulation protocols can in fact induce plasticity.

Conclusion

tACS has the potential to enhance cognitive functioning by modulating rhythmic cortical activity within and between cortical areas. tACS seems to be more effective when applied at the individual endogenous frequency pointing to the necessity to tailor tACS frequency to the individual needs. In particular, theta tACS seems to support WM performance, whereas beta tACS sustains motor learning, and alpha and gamma tACS are more related to visual perception and creativity.

However, much more research has to be done to improve our knowledge about the enhancing effects of tACS on cognition and how to optimize stimulation protocols (e.g., intensity and duration of the stimulation, electrode size and number, scalp placement). It is important to acknowledge that extensive research is needed to verify whether the observed tACS-enhanced cognitive effects are preserved over time. Previous studies have shown that repetitive sessions of tDCS can increase the effects of stimulation (Nitsche and Paulus 2011), but it remains to be established whether the same applies to tACS. Hence, future studies assessing the impact of multiple stimulation sessions and the risk of incurring potential side-effects are necessary. Although more research is needed to fully understand the effects tACS exert on cognition at long term, we conclude that, tACS is a promising tool for enhancing cognitive functions.

References

Ali, M. M., Sellers, K. K., & Fröhlich, F. (2013). Transcranial alternating current stimulation modulates large-scale cortical network activity by network resonance. *Journal of Neuroscience, 33*(27), 11262–11275.

Antal, A., Boros, K., Poreisz, C., Chaieb, L., Terney, D., & Paulus, W. (2008). Comparatively weak after-effects of transcranial alternating current stimulation (tACS) on cortical excitability in humans. *Brain Stimulation, 1*(2), 97–105.

Antal, A., & Paulus, W. (2013). Transcranial alternating stimulation (tACS). *Frontiers in Human Neuroscience, 7,* 1–4.

Baer, J. (1993). *Creativity and divergent thinking: A task-specific approach*. Hillsdale, NJ: Lawrence Erlbaum Associates.

Battleday, R. M., Muller, T., Clayton, M. S., & Cohen Kadosh, R. (2014). Mapping the mechanisms of transcranial alternating current stimulation: A pathway from network effects to cognition. *Frontiers in Psychiatry, 5,* 1–5.

Bikson, M., Datta, A., Rahman, A., & Scaturro, J. (2010). Electrode montages for tDCS and weak transcranial electrical stimulation: Role of "return" electrode's position and size. *Clinical Neurophysiology, 121,* 1976–1978.

Cabral-Calderin, Y., Schmidt-Samoa, C., & Wilke, M. (2015). Rhythmic gamma stimulation affects bistable perception. *Journal of Cognitive Neuroscience, 27*(7), 1298–1307. doi:10.1162/jocn_a_00781

Cecere, R., Rees, G., & Romei, V. (2015). Individual difference in alpha frequency drive crossmodal illusory perception. *Current Biology, 25,* 231–235.

Chaieb, L., Antal, A., & Paulus, W. (2011). Transcranial alternating current stimulation in the low kHz range increases motor cortex excitability. *Restorative Neurology and Neuroscience, 29*(3), 167–175.

Cohen Kadosh, R. (2015). Modulating and enhancing cognition using brain stimulation: Science and fiction. *Journal of Cognitive Psychology, 27*(2), 141–163.

Fink, A., & Benedek, M. (2014). EEG alpha power and creative ideation. *Neuroscience and Biobehavioral Reviews, 44,* 111–123.

Fink, A., Benedek, M., Grabner, R. H., Staudt, B., & Neubauer, A. C. (2007). Creativity meets neuroscience: Experimental tasks for the neuroscientific study of creative thinking. *Methods, 42,* 68–76.

Fröhlich, F. (2014). Endogenous and exogenous electric fields as modifiers of brain activity: Rational design of noninvasive brain stimulation with transcranial alternating current stimulation. *Dialogues in Clinical Neuroscience, 16*(1), 93–102.

Fröhlich, F., Sellers, K. K., & Cordle, A. L. (2014). Targeting the neurophysiology of cognitive systems with transcranial alternating current stimulation. *Expert Review of Neurotherapeutics, 15*(2), 145–167.

Helfrich, R. F., Knepper, H., Nolte, G., Strüber, D., Rach, S., Herrmann, C. S. … Engel, A. K. (2014a). Selective modulation of interhemispheric functional connectivity by HD-tACS shapes perception. *PLoS Biology, 12*(12), 1–15.

Helfrich, R. F., Schneider, T. R., Rach, S., Trautmann-Lengsfeld, S. A., Engel, A. K., & Herrmann, C. S. (2014b). Entrainment of brain oscillations by transcranial alternating current stimulation. *Current Biology, 24,* 333–339.

Herrmann, C. S., Strüber, D., Helfrich, R. F., & Engel, A. K. (2015). EEG oscillations: From correlation to causality. *International Journal of Psychophysiology, 103,* 12–21.

Iacono, M. I., Neufeld, E., Akinnagbe, E., Bower, K., Wolf, J., Vogiatzis Oikinomidis, I., … Angelone, L. M. (2015). MIDA: A multimodal imaging-based detailed anatomical model of the human head and neck. *PLoS ONE, 10*(4), 1–35.

Janik, A., Rezlescu, C., & Banissy, M. J. (2015). Enhancing anger perception with transcranial alternating current stimulation induced gamma oscillations. *Brain Stimulation, 8*(6), 1138–1143.

Jauk, E., Benedek, M., & Neubauer, A. C. (2012). Tackling creativity at its roots: Evidence for different patterns of EEG alpha activity related to convergent and divergent modes of task processing. *International Journal of Psychophysiology, 84*(2), 219–225.

Jaušovec, N., & Jaušovec, K. (2014). Increasing working memory capacity with theta transcranial alternating current stimulation (tACS). *Biological Psychology, 96*, 42–47. doi:10.1016/j.biopsycho.2013.11.006

Jaušovec, N., Jaušovec, K., & Pahor, A. (2014). The influence of theta transcranial alternating current stimulation (tACS) on working memory storage and processing functions. *Acta Psychologica, 146,* 1–6.

Kanai, R., Chaieb, L., Antal, A., Walsh, P., & Paulus, W. (2008). Frequency-dependent electrical stimulation of the visual cortex. *Current Biology, 18,* 1839–1843.

Kar, K., & Krekelberg, B. (2014). Transcranial alternating current stimulation attenuates visual motion adaptation. *Journal of Neuroscience, 34*(21), 7334–7340.

Kim, K. H. (2006). Can we trust creativity tests? A review of the Torrance tests of creative thinking (TTCT). *Creativity Research Journal, 18*(1), 3–14.

Krause, B., & Cohen Kadosh, R. (2014). Not all brains are created equal: The relevance of individual differences in responsiveness to transcranial electrical stimulation. *Frontiers in Systems Neuroscience, 8,* 1–12.

Kuo, M.-F., & Nitsche, M. A. (2015). Exploring prefrontal cortex functions in healthy humans by transcranial electrical stimulation. *Neuroscience Bulletin, 31*(1), 198–206.

Laczó, B., Antal, A., Niebergall, R., Treue, S., & Paulus, W. (2012). Transcranial alternating stimulation in a high gamma frequency range applied over V1 improves contrast perception but does not modulate spatial attention. *Brain Stimulation, 5*(4), 484–491.

Lisman, J. E., & Jensen, O. (2013). The theta-gamma neural code. *Neuron, 77*(6), 1006–1016.

Lustenberger, C., Boyle, M. R., Foulser, A. A., Mellin, J. M., & Fröhlich, F. (2015). Functional role of frontal alpha oscillations in creativity. *Cortex, 67,* 74–82.

Mehta, A. R., Pogosyan, A., Brown, P., & Brittain, J.-S. (2015). Montage matters: The influence of transcranial alternating current stimulation on human physiological tremor. *Brain Stimulation, 8*(2), 260–268.

Meiron, O., & Lavidor, M. (2014). Prefrontal oscillatory stimulation modulates access to cognitive control references in retrospective metacognitive commentary. *Clinical Neurophysiology, 125,* 77–82.

Moliadze, V., Antal, A., & Paulus, W. (2010). Boosting brain excitability by transcranial high frequency stimulation in the ripple range. *Journal of Physiology, 588*(24), 4891–4904.

Moliadze, V., Atalay, D., Antal, A., & Paulus, W. (2012). Close to threshold transcranial electrical stimulation preferentially activates inhibitory networks before switching to excitation with higher intensities. *Brain Stimulation, 5*(4), 505–511.

Neuling, T., Rach, S., & Herrmann, C. S. (2013). Orchestrating neuronal networks: Sustained after-effects of transcranial alternating current stimulation depend upon brain states. *Frontiers in Human Neuroscience, 7,* 1–12.

Neuling, T., Ruhnau, P., Fuscà, M., Demarchi, G., Herrmann, C. S., & Weisz, N. (2015). Friends, not foes: Magnetoencephalography as a tool to uncover brain dynamics during transcranial alternating current stimulation. *NeuroImage, 118,* 406–413.

Neuling, T., Wagner, S., Wolters, C. H., Zaehle, T., & Herrmann, C. S. (2012). Finite-element model predicts current density distribution for clinical applications of tDCS and tACS. *Frontiers in Psychiatry, 3,* 1–10.

Nitsche, M. A., Cohen, L. G., Wassermann, E. M., Priori, A., Lang, N., Antal, A. … Pascual-Leone, A. (2008). Transcranial direct current stimulation: State of the art 2008. *Brain Stimulation, 1*(3), 206–223.

Nitsche, M.A., Doemkes, S., Karakoese, T., Antal, A., Liebetanz, D. … Paulus, W. (2007). Shaping the effects of transcranial direct current stimulation of the human motor cortex. *Journal of Neurophysiology*, *97*, 3109–3117.

Nitsche, M. A., & Paulus, W. (2011). Transcranial direct current stimulation—update 2011. *Restorative Neurology and Neuroscience, 29,* 463–492.

Paulus, W. (2011). Transcranial electrical stimulation (tES—tDCS; tRNS; tACS) methods. *Neuropsychological Rehabilitation, 21*(5), 602–617.

Polanía, R., Nitsche, M. A., Korman, C., Batsikadze, G., & Paulus, W. (2012). The importance of timing in segregated theta phase-coupling for cognitive performance. *Current Biology, 22*(14), 1314–1318.

Pollock, V., Schneider, L., & Lyness, S. (1991). Reliability of topographic quatitative EEG amplitude in healthy late middle ages and elderly subjects. *Electroencephalography and Clinical Neurophysiology, 79*(1), 20–26.

Pollok, B., Boysen, A.-C., & Krause, V. (2015). The effect of transcranial alternating current stimulation (tACS) at alpha and beta frequency on motor learning. *Behavioural Brain Research, 293,* 234–240.

Radman, T., Ramos, R. L., Brumberg, J. C., & Bikson, M. (2009). Role of cortical cell type and morphology in subthreshold and suprathreshold uniform electric field stimulation in vitro. *Brain Stimulation, 2,* 215–228.

Reato, D., Rahman, A., Bikson, M., & Parra, L. C. (2010). Low-intensity electrical stimulation affects network dynamics by modulating population rate and spike timing. *Journal of Neuroscience, 30*(45), 15067–15079.

Reato, D., Rahman, A., Bikson, M., & Parra, L. C. (2013). Effects of weak transcranial Alternating Current Stimulation on brain activity—A review of known mechanisms. *Frontiers in Human Neuroscience, 7,* 1–8.

Roux, F., & Uhlhaas, P. J. (2014). Working memory and neural oscillations: Alpha–gamma versus theta–gamma codes for distinct WM information? *Trends in Cognitive Sciences, 18*(1), 16–25.

Ruffini, G., Fox, M. D., Ripolles, O., Miranda, P. C., & Pascual-Leone, A. (2014). Optimization of multifocal transcranial current stimulation for weighted cortical pattern targeting from realistic modeling of electric fields. *Neuroimage, 89,* 216–225.

Ruffini, G., Wendling, F., Merlet, I., Molaee-Ardekani, B., Mekkonen, A., Salvador, R. … Miranda, P. C. (2013). Transcranial current brain stimulation (tCS): Models and technologies. *IEEE Transactions on Neural Systems and Rehabilitation Engineering, 21*(3), 333–345.

Schaal, N. K., Pfeifer, J., Krause, V., & Pollok, B. (2015). From amusic to musical?—Improving pitch memory in congenital amusia with transcranial alternating current stimulation. *Behavioural Brain Research, 294,* 141–148.

Schmidt, S. L., Iyengar, A. K., Alban Foulser, A., Boyle, M. R., & Fröhlich, F. (2014). Endogenous cortical oscillations constrain neuromodulation by weak electric fields. *Brain Stimulation, 7,* 879–889.

Shams, L., Kamitani, Y., & Shimojo, S. (2000). Illusions: What you see is what you hear. *Nature, 408,* 788.

Stassen, H. H., Bomben, G., & Propping, P. (1987). Genetic aspects oft he EEG: An investigation into the within-pair similarity of monozygotic and dizygotic twins with a new method of analysis. *Electroencephalography and Clinical Neurophysiology, 66*(6), 489–501.

Strüber, D., Rach, S., Neuling, T., & Herrmann, C. S. (2015). On the possible role of stimulation duration for after-effects of transcranial alternating current stimulation. *Frontiers in Cellular Neuroscience, 9,* 1–7.

Thut, G., & Miniussi, M. (2009). New insights into rhythmic brain activity from TMS-EEG studies. *Trends in Cognitive Sciences, 13*(4), 182–189.

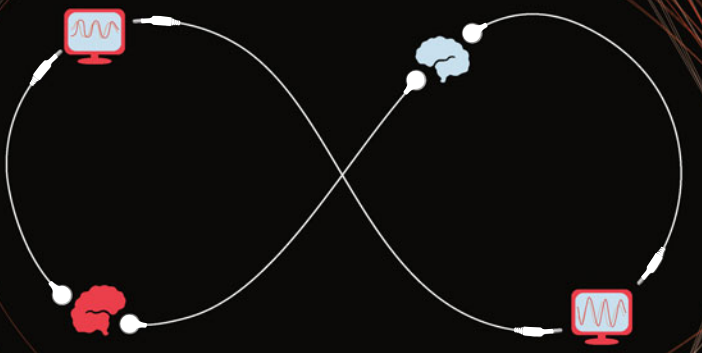
Van Wezel, R. J., & Britten, K. H. (2002). Motion adaptation in area MT. *Journal of Neurophysiology, 88*(6), 3469–3476.

Voss, U., Holzmann, R., Hobson, A., Paulus, W., Koppehele-Gossel, J., Klimke, A., et al. (2014). Induction of self-awareness in dreams through frontal low current stimulation of gamma activity. *Nature Neuroscience, 17*(6), 810–814.

Vossen, A., Gross, J., & Thut, G. (2015). Alpha power increase after transcranial alternating current stimulation at alpha frequency (α-tACS) reflects plastic changes rather than entrainment. *Brain Stimulation, 8*(3), 499–508.

Vosskuhl, J., Huster, R. J., & Herrmann, C. S. (2015). Increase in short-term memory capacity induced by down-regulating individual theta frequency via transcranial alternating current stimulation. *Frontiers in Human Neuroscience, 9,* 1–10.

neurofeedback



Neurofeedback

Stefanie Enriquez-Geppert, René J. Huster,
Tomas Ros and Guilherme Wood

Introduction

Already at the earliest recordings of the human EEG, the rhythmic and repetitive brain activity was one consistent detected feature (Berger 1929). As EEG time–frequency decomposition reveals, such rhythmic activity has been shown at different frequencies, ranging from delta (0–4 Hz) to gamma (30–100 Hz). Furthermore, these brain rhythms have been observed throughout different levels of neural organization, ranging from single-neuron activity, to local activity of neuronal groups, and even to activity among cortical networks of different brain areas (e.g., Buzsáki et al. 2013). These days, the study of brain oscillations is attracting substantial amount of scientific attention and is one of the fastest growing research areas in neuroscience. Oscillations represent a major mechanism of communication within the brain (Buzsáki et al. 2013) and have been consistently related to cognitive functions (e.g., Başar and Güntekin 2008; Herrmann and Knight 2001). An example of such an association is the link between frontal-midline (fm) theta

S. Enriquez-Geppert (✉)
Department of Clinical and Developmental Neuropsychology,
Faculty of Behavioural and Social Sciences, University of Groningen,
Grote Kruisstraat 2/1, 9712 TS Groningen, The Netherlands
e-mail: s.enriquez.geppert@rug.nl

R.J. Huster
Department of Psychology, University of Oslo, Oslo, Norway

T. Ros
Laboratory for Neurology and Imaging of Cognition, Department of Neurosciences,
University of Geneva, Geneva, Switzerland

G. Wood
Department of Neuropsychology, University of Graz, Graz, Austria

L.S. Colzato, *Theory-Driven Approaches to Cognitive Enhancement*,
DOI 10.1007/978-3-319-57505-6_11

oscillations and executive control (Cavanagh and Frank 2014). Executive control refers to higher order functions that subserve a variety of psychological phenomena to enable adaptive and goal-oriented behavior. Fm-theta oscillations are event-related (Klimesch 1999), typically recorded over fronto-medial brain regions (Ishihara et al. 1981) and generated in the midcingulate cortex (MCC) (e.g., Cavanagh and Frank 2014). Within the network implementing executive functions (Niendam et al. 2012), the MCC is suggested to serve as a neuronal hub (Cavanagh et al. 2012). Power increases of fm-theta have been associated with enhanced cognitive processing (Mitchell et al. 2008) and can predict successful behavioral performance (Sederberg et al. 2003; Cohen and Donner 2013). Accordingly, the absence of such fm-theta power enhancements is related to reduced behavioral and cognitive performance (e.g., Donkers et al. 2011).

Mechanism of Action

Endogenous neural oscillations that show a theoretically and empirically confirmed relation to a specific cognitive function represent a direct target for the enhancement of cognition with neuroscientific approaches in general, such as neurofeedback and transcranial alternating current stimulation (tACS). However, and to put it simply, whereas tACS is an approach applying exogenous oscillations to affect endogenous neural oscillations (see Chapter "Transcranial Alternating Current Stimulation"), the goal of neurofeedback is the self-regulation of endogenous neural oscillations. Here, neural parameters of ongoing neural activity are fed back to the participant on a trial-by-trial fashion to up- or downregulate one's own brain activity (e.g., Huster et al. 2014). Thereby implementation of neurofeedback is realized by a software system and a processing pipeline consisting of five basic elements, including data acquisition, online data processing, online feature extraction, online feedback generation, and the learning participant (see Huster et al. 2014; Enriquez-Geppert et al., subm.), see Fig. 1.

Enhancement of Cognition by Neurofeedback

Based on the above-described associations of fm-theta and executive functions, neurofeedback studies have been set up. In these studies, fm-theta is extracted as scalp activity measured at mid-frontal electrodes. In one such investigation, it has been demonstrated that fm-theta neurofeedback indeed led to enhanced performance in two particular executive functions, namely task-switching and memory-updating (Enriquez-Geppert et al. 2014). In a further study, cognitive enhancements have also been shown in the domain of working memory in the elderly (Wang and Hsie 2014).

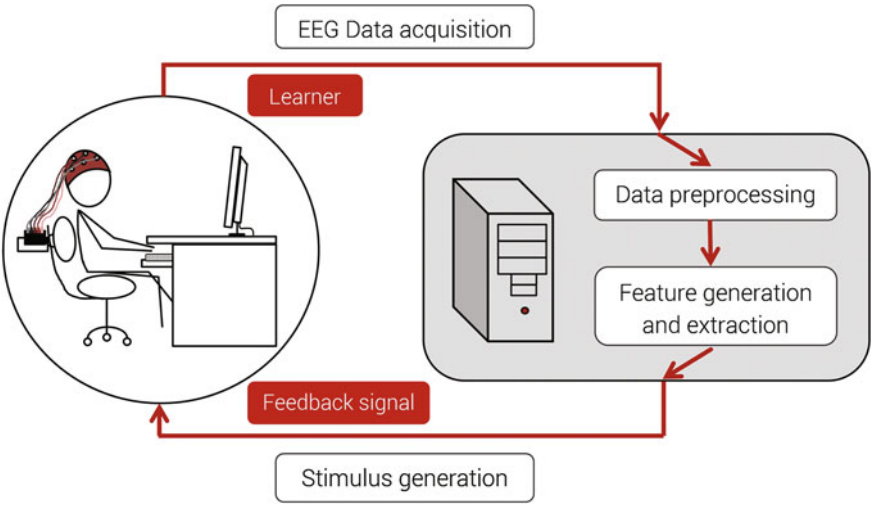


Fig. 1 Basic setup of a brain–computer interface for neurofeedback. After recording of EEG, data undergo preprocessing (e.g., artifact detection and rejection or correction), feature generation and extraction, computation, and presentation of the feedback signal. The latter step closes the feedback loop, with the participant trying to learn to use the feedback signal to alter the brain activity in accordance with the instructions

However, a considerable amount of literature reported associations of alpha oscillations with cognition, specifically focusing on the upper alpha sub-band (for a review, see Klimesch 1999). On the basis of such findings, alpha neurofeedback studies were conducted and effects were shown such as enhanced mental rotation capacity (e.g., Hanslmayr et al. 2005; Zoefel et al. 2010), as well as increased short-term memory performance (e.g., Escolano et al. 2011; Nan et al. 2012). Recently, Hsueh et al. (2016) presented evidence for an association between the amount of self-regulation capacity after neurofeedback and the amount of performance changes on cognition. Those participants who gained specifically good self-control of alpha brain activity were also those improving most regarding performance on working and episodic memory. Guez et al. (2014) performed a sham-controlled, double-blind neurofeedback study and demonstrated dissociations of two different protocols on different memory processes. Upper alpha frequency training led to enhanced strategic and top-down processes as reflected in associative memory, whereas training of the sensory motor rhythm (SMR, 13–15 Hz) led to enhanced performance in less-effortful and less-strategic memory task as reflected in improved item memory (Guez et al. 2014, see but also Kober et al. 2015a, b).

Apart from associations with working memory, alpha brain oscillations are linked to covert attention. In situations in which attention is either directed to the left or right visual hemifield, concurrent enhanced alpha is observed in the ipsilateral hemisphere, while alpha power is reduced in the contralateral hemisphere (e.g., van Gerven and Jensen 2009; Rihs et al. 2007).

Moreover, the strength of hemispheric alpha lateralization has been found to correlate with behavioral performance (Horschig et al. 2014; Thut et al. 2006). Resting upon these associations, Okazaki et al. (2015) gave their participants feedback on their posterior alpha lateralization, while they kept their attention to either the left or right hemifield. Indeed, neurofeedback training transferred to short-term changes in visual detection performance. SMR has also been observed during light non-rapid eye movement (REM) sleep, as represented by the so-called sleep spindles, which are generated in thalamo-cortical circuits (Steriade 1999). In an animal model, it was shown that learning to change SMR by conditioning transferred to facilitated sleep spindle bursts and enhanced sleep quality (Sterman et al. 1970). Thus, Hoedlmoser et al. (2008) performed an SMR neurofeedback study to investigate the effects on sleep spindles and memory consolidation in humans and demonstrated effects on memory retrieval.

Regarding high-frequency bands in the domain of gamma oscillations, evidence suggests associations to visual local feature integration, binding, as well as to visual short-term memory (Tallon-Baudry and Bertrand 1999; Engel and Singer 2001). In studies conducted by Keizer et al. (2010a, b), participants learned to either upregulate their gamma band activity or to decrease their beta activity. Enhanced performance in feature integration was shown after gamma neurofeedback training, as was reflected in reduced binding costs.

Altogether, these results provide support that the modulation of endogenous oscillations is possible by neurofeedback and that such self-regulation transfers to enhanced cognition. For further readings about cognitive outcomes after neurofeedback see the review provided by Gruzelier (2014a).

Effects of Neurofeedback on Everyday Life Performance

Apart from the investigation of neurofeedback effects on cognition, studies have been conducted to investigate transfer to everyday life performance. For instance, Ros et al. (2009) trained ophthalmic microsurgeons with SMR neurofeedback training. With this study, participants demonstrated improved surgical skills after learned self-regulation of SMR as rated by experts regarding the overall surgery technique on the one hand, and shown on the other hand by increased performance in a suture task. SMR is also related to a maintained relaxed, but focused state, which is probably due to the reduction of motor perception processes of the sensorimotor cortex (Vernon et al. 2003). Thus, neurofeedback studies have also been conducted for sport performance, such as golfing (e.g., Arns et al. 2008). Cheng et al. (2015) investigated a sham-controlled SMR training with pre-elite golfers. Indeed, self-regulation of SMR in neurofeedback transferred to enhanced SMR power during action preparation while golfing, but crucially also to increased golf putting performance. However, as studies reported of specific brain activity such as the suppression of high alpha power immediately before successful movement

initiation for striking putts (Babiloni et al. 2008; Cooke et al. 2014), the down-regulation of alpha activity in golfers might depict a further possible neurofeedback protocol (Ring et al. 2015).

A further range of neurofeedback studies analyzing the effects on real-life performance has been performed in the domain of creativity in the arts (see for a review Gruzelier 2014b). Here, so-called alpha–theta trainings arose. These are based on mainly two associations of oscillations and cognition: first, alpha activity and its association with low arousal and diffuse attention (e.g., Fink and Neubauer 2006; Grabner et al. 2007; Bazanova and Aftenas 2008) and second, oscillations in the theta domain observed in states between waking and sleeping, which are supposed to ease creative processes (Schachter 1976). The alpha–theta training is typically conducted while participants close their eyes and learn to increase their posterior theta relative to alpha amplitudes. This protocol has been found to lead to enhanced music performance in professional musicians regarding their artistic expression (e.g., Egner and Gruzelier 2004), but also increased performance of novice musicians (Gruzelier et al. 2014a). Similarly, this alpha–theta protocol increased dancing performance of professional dancers (Raymond et al. 2005; Gruzelier et al. 2014b).

We will now turn to the conceptualization of self-control of brain activity and the underlying mechanism of changes in cognition and behavior induced by neurofeedback.

Conceptualization of Self-control of Brain Activity

Generally, a circuit involving the anterior insula, middle frontal gyrus, anterior dorsal cingulate gyrus has been identified that is responsible for these more general aspects of cognitive control that are activated equally by sham (Ninaus et al. 2013, 2015) as well as effective neurofeedback (Emmert et al. 2016). Moreover, basal ganglia structures such as the striatum have been related to the core learning processes occurring during neurofeedback (Birbaumer et al. 2013). Neurofeedback learning is more complex in humans than in typical animal models that are highly motivated by deprivation and rewarded with primary reinforcement. Humans have a much richer and active mind than other animals. As such, task models, strategies, verbalizations, self-referential processes, visual, sensorial, and emotional imagery, etc. may bias or even hamper more basic procedural learning in humans and can only be switched on or off by means of purposeful cognitive control (Wood et al. 2014). Therefore, control of brain activity during neurofeedback is more than merely learning to regulate the activity in one specific neural network that is targeted directly by neurofeedback. Neurofeedback learning also involves the ability to tune the activity in other large-scale networks that are not related to the production of the brain signal being trained but can hamper the learning process (Wood et al. 2014). Accordingly, neurofeedback learning seems to be more complex than mere procedural learning and rather the result of conjugated labor of different brain

networks (Wood et al. 2014) tuned to optimize the control of the specific brain signals under training by means of feedback, thereby giving rise to different forms of brain plasticity (Ros et al. 2014).

Neuroplastic Effects of Neurofeedback

Theoretically, the observation of voluntary control of particular measure(s) of brain function (e.g., spectral power) is in itself independent of demonstrating an impact on its plasticity. For neurofeedback, and in analogy to general learning, plasticity implies a progressive and long-term change—of at least >20–30 min (Schulz and Fitzgibbons 1997)—of a measure during or after training. From a historical perspective, seminal experiments in the 1960s reporting online control of the EEG (Kamiya 2011; Sterman et al. 1969) were followed by evidence that waking SMR may be operantly conditioned to be more strongly expressed during subsequent sleep (Sterman et al. 1970). This observation of oscillatory patterns may be modified by neurofeedback within and/or between training sessions, has now been confirmed by a collection of studies, and reported to apply to theta upregulation (Enriquez-Geppert et al. 2013; Sittenfeld et al. 1976) and downregulation (Lubar and Swartwood 1995; Monastra et al. 2002; Janssen et al. 2016), alpha upregulation (Cho et al. 2008; Zoefel et al. 2010; Escolano et al. 2011) and downregulation (Ros et al. 2013; Ros et al. 2010; Regestein et al. 1973), beta upregulation (Engelbregt et al. 2016; Staufenbiel et al. 2014), and gamma upregulation (Keizer et al. 2010). What remains unclear is the physiological mechanism responsible for the plasticity of these oscillatory patterns. Given that the effects manifest in the same direction as dictated by the neurofeedback protocol, a candidate mechanism may be Hebbian plasticity, often summarized by the phrase: "synapses that fire together wire together, and synapses that fire apart wire apart". This type of associative plasticity occurs when neuronal patterns are reinforced by functional association in time, and may be explained by the fact that EEG oscillatory amplitude positively covaries with the number of synchronized neurons/synapses (Musall et al. 2014). Consequently, during amplified oscillations, the population(s) of neurons which are coherently involved in generating an oscillatory pattern would, after some time, further strengthen the connections between themselves, thus making it easier for this population pattern to emerge in the future (Knoblauch et al. 2012). Conversely, maintaining a group of neurons in a prolonged desynchronized state would weaken the correlated firing of their synapses and attenuate the connections that give rise to synchronization. This mode of action is supported by several modeling studies of Hebbian spike-timing-dependent plasticity (STDP) (Knoblauch et al. 2012; Pfister and Tass 2010; Legenstein et al. 2008), as well as in vivo experiments demonstrating lasting synchronization (Zaehle et al. 2010; Vossen et al. 2015) and desynchronization (Tass et al. 2009; Adamchic et al. 2014) of cortical oscillations using endogenous patterns of stimulation.

On the other hand, another body of research points to the existence of a complementary form of plasticity which is anti-Hebbian, or homeostatic (Hulme et al. 2013). This appears to be the consequence of intrinsic regulatory mechanisms that prevent brain activities reaching extremes, such as pathologically high/low synaptic strengths or oscillatory states (Whitt et al. 2013; Fauth and Tetzlaff 2016). Put succinctly, this form of plasticity produces changes in the very opposite direction of training (or what could be expected from Hebbian mechanisms). One of the first observations within the context of neurofeedback was made by Kluetsch et al. (2014), who reported a paradoxical rebound of spontaneous alpha rhythm following its down-training in patients with post-traumatic stress disorder (PTSD). Since these patients were found to exhibit significantly low alpha amplitude at baseline relative to healthy subjects, it was proposed that this might well be a homeostatic response (Kluetsch et al. 2014) and/or the brain self-organizing to criticality by tuning its excitation/inhibition ratio (Ros et al. 2016). The latter interpretation was based on the significant recovery of scale-free alpha amplitude fluctuations (Ros et al. 2016), as well as prior evidence that neurofeedback alpha downregulation could enhance cortical excitability and lower intracortical inhibition, as measured by a lasting increase of transcranial magnetic stimulation (TMS) motor-evoked potentials.

Finally, EEG neurofeedback-induced plasticity has also been investigated using a different set of modalities, including functional magnetic resonance imaging (fMRI) and diffusion tensor imaging (DTI). fMRI has shown that neurofeedback may lead to plastic changes in cortical regions responsible for cognitive control such as the anterior cingulate, associated with improvements in attention-deficit (Lévesque et al. 2006) or on-task mind wandering (Ros et al. 2013). DTI has yielded data that makes a promising case for neurofeedback impacting white matter pathways, in addition to changes in gray matter volume (Ghaziri et al. 2013). Taken together, this collective work indicates a basis for harnessing neurofeedback as a neuroplasticity-based technique in health and disease.

Interindividual Differences in Neurofeedback: Responders and Nonresponders

The investigation on responders vs nonresponders is a subtopic of the more general question of individual differences in neurofeedback. While review papers are full of examples of positive neurofeedback effects, only a few studies so far have investigated negative effects of neurofeedback systematically (e.g., Kober et al. 2015a). About 15–30% of participants do not show neurofeedback learning in EEG-based studies. Such estimates have not been reported yet for other brain signals such as the blood-oxygen-level-dependent (BOLD) response, but there are reports suggesting that responsivity to real-time fMRI feedback training is higher than 70%. One may distinguish at least four reasons for individual variability in the responsivity to neurofeedback, which are the following:

Physical reasons: Signal detection can be poor because of anatomical abnormalities or idiosyncrasy (Allison and Neuper 2010). EEG signal power can show dramatic variation depending on the position of the brain relative to electrodes (Rice et al. 2013). Accordingly, movement artifacts as well as brain shape may change the individual responsivity neurofeedback.

Physiological reasons: In a recent study, predictors of performance in a SMR frequency EEG neurofeedback were investigated. Findings indicate that more than age or sex, SMR signal intensity is predictive of poor learning (Reichert et al. 2016a). Participants with lower levels of SMR power over the central electrodes were less able to learn to increase the SMR power along the course of 10 training sessions.

Cognitive reasons: Reserve capacity may boost the effect of neurofeedback training (Reichert et al. 2016b, c). Some people adept some specific concentration practices seem to be more able to regulate their internal environment and to benefit more from neurofeedback learning. In a recent study, 28 triathletes learned more during even a single session of neurofeedback training than 28 matched healthy controls (Witte 2015). Accordingly, 20 Christian participants adept of intensive praying also learn more during a single session of neurofeedback than 20 matched controls (Kober et al. 2015c). A recent study also indicates that mindfulness may facilitate neurofeedback learning (Kikkert 2015).

Metacognitive reasons: Levels of perceived locus of control toward technology predict learning (Witte et al. 2013). Spontaneous strategies are associated with learning success (Kober et al. 2013). The length in words of the learning protocols of young healthy participants correlates with learning effects. The more succinct the answer to the question "what have you being doing during neurofeedback training", the better are the training outcomes ($r(65) = 0.4$, unpublished data). These pieces of evidence suggest that the individual task model (i.e., "how do I solve the task of learning from neurofeedback?") is in part responsible for individual training outcomes. The more graspable the contents of the training instructions for individuals, the more consistent are the results across individuals. Neurofeedback training protocols based on some form of mental imagery that can be easily understood and uniformly implemented will therefore also produce more uniform results than neurofeedback protocols based on some less-specific mental state such as for instance "being relaxed but concentrated". Interestingly, some brain signals seem to respond better to training when instructions are vaguer and cannot be forced to respond to a specific set of instructions (Hardman et al. 1997).

Specificity and Efficacy

The discussion about nonresponders can also be embedded in a somewhat larger context, namely when addressing those factors that determine the overall efficacy of neurofeedback. What factors constitute a training that maximizes the pre- to post-changes in neural parameters and behavioral performance measures? Whereas

there is no definitive answer to this question (yet), it is worthwhile considering some factors most likely contributing to neurofeedback efficacy. Since neurofeedback usually aims at the enhancement of a specific cognitive function, it seems straightforward to optimize those neural systems and processes that give rise to these cognitive processes. EEG-based protocols usually try to achieve this by extracting the activity of one or two frequency bands from a selected number of electrodes and instructing the participants to up- or downregulate the amplitude or the activity ratio of these bands (Gruzelier 2014c). As mentioned earlier, substantial interindividual differences in brain morphology may obscure the purity of so-derived features, as does the fact that it is rather unlikely that cognitive components can easily be tied to such narrowly defined features alone. Current approaches thus neglect the many facets of neural signals that have meanwhile been linked to cognition, such as cross-frequency coupling, inter-regional communication, and gross brain connectivity as inferred from large-scale connectivity analyses (e.g., Sauseng and Klimesch 2008; Sporns 2014). Similarly, neurofeedback could be optimized further with regards to maximizing the effects in terms of neural plasticity discussed earlier, and it is likely that induced plasticity closely relates to those neural mechanisms providing the underpinnings of cognitive processes in the first place. To date it is largely unclear how to best address any given neural system and its means of neural communication. For example, what would maximize neurofeedback efficacy aiming at cognitive control: The upregulation of fm-theta alone, or the maximization of the theta-to-alpha ratio? Such comparative studies are needed for every targeted process, yet they seem to be hardly ever conducted. Exhibiting the relevance of such work, Salari et al. (2013) found that neurofeedback for both alpha and gamma upregulation enhanced object-recognition, but object detection was more strongly influenced by the gamma-based training. Another approach to increase neurofeedback specificity, i.e., the ability to modulate the targeted system alone, may be to compute feedback in the source rather than the electrode space. Note that any recording of EEG activity at a given electrode, even that within well-circumscribed frequency bands, always reflects the activity summed across many different brain regions. Thus, combining frequency-specific feedback with EEG source analyses may well minimize the influence of cross-talk from other brain networks in our feedback signal, thereby potentially optimizing neurofeedback efficacy. A number of studies have been conducted following this notion, all combining Low Resolution Tomography (LORETA) for EEG inverse modeling with feedback based on alpha or beta activity as extracted from the midcingulate region (e.g., Congedo et al. 2004; Cannon et al. 2007, 2009; Maurizio et al. 2014). A conceptually similar methodology was tested by Zotev et al. (2011, 2014), who combined EEG feedback of beta band activity with simultaneously recorded activations of the amygdala as measured via fMRI. The common element of all these studies is that increased neurofeedback specificity may be achieved by enriching standard EEG frequency features through spatial filters. Yet again, comparative studies are needed to assess whether increases specificity indeed leads to increased efficacy of neurofeedback.

Another group of factors likely to affect neurofeedback efficacy does not so much relate to neural processes per se, but rather to the optimization of training designs in accordance with principles underlying basic learning mechanisms. For example, whereas some studies do report that significant feedback-related learning may already be found after a single training session, the majority of studies seem to indicate that reliable training effects occur after about ten training sessions (see Gruzelier 2014c, for a review). Also, established work on reinforcement schedules would suggest that a relatively early transition from continuous to intermittent reinforcement would optimize training outcome, yet this notion has not yet been tested in context of neurofeedback. This issue does relate to both the temporal spacing of feedback signals within a single session (e.g., continuous feedback vs. blocked feedback) and the scheduling of training sessions across days and weeks. Neither of these two phenomena has yet been tested systematically, although the notion that neural plasticity through synaptic consolidation and reorganization need time clearly supports the validity of these basic learning mechanisms also in neurofeedback contexts. Again, however, systematic studies are missing and only rather anecdotal evidence is available in favor of this notion (e.g., Schabus et al. 2014).

Conclusion

A necessary basis for the enhancement of cognitive functions with neuroscientific approaches are theoretically and empirically confirmed associations of brain activity and cognition. By feeding back neural parameters of ongoing neural activity to the participants on a trial-by-trial fashion, self-regulation of brain activity can be achieved. The self-control of brain activity in humans has been suggested to be more complex than in the animal model, and to exceed mere procedural learning. Thus, different brain networks might be engaged to adjust control over a brain signal during neurofeedback training. Regarding the physiological mechanism responsible for neurofeedback-induced plasticity, which might even impact brain morphology; two forms are in focus, (1) Hebbian/associative plasticity and a complementary form, which is known as (2) anti-Hebbian/homeostatic plasticity. Regarding the responsivity to neurofeedback large individual variability has been reported and four different reasons have been suggested to play a role. Notable are physical (poor signal detection), physiological (initial signal intensity of the brain feature), cognitive (reserve capacity), and metacognitive reasons (training instructions and strategies of self-regulation). The responsiveness to neurofeedback and hence its efficacy may further be moderated by methodological factors. One such group of factors considers how to best address a given neural system and its means of communication. Here, the combination of frequency-specific feedback with EEG source analysis offers one approach. A further group of factors focuses on the optimization of training designs that follow the principles of basic learning mechanisms. Thus, whereas many factors can be derived from our knowledge on

the neural underpinnings of cognition, available measurement techniques, as well as basic learning mechanisms, much more systematic work needs to be conducted to optimize neurofeedback protocols for basic research and clinical applications.

References

Adamchic, I., Toth, T., Hauptmann, C., & Tass, P. A. (2014). Reversing pathologically increased EEG power by acoustic coordinated reset neuromodulation. *Human Brain Mapping, 35*(5), 2099–2118. doi:10.1002/hbm.22314

Allison, B., & Neuper, C. (2010). Could anyone use a BCI? In D. Tan & A. Nijholt (Eds.), *Brain–Computer Interfaces: Human–Computer Interaction Series* (pp. 35–54). London: Springer. doi:10.1007/978-1-84996-272-8_3

Arns, M., Kleinnijenhuis, M., Fallahpour, K., & Breteler, R. (2008). Golf performance enhancement and real-life neurofeedback training using personalized event-locked EEG profiles. *Journal of Neurotherapy, 11*(4), 11–18. doi:10.1080/10874200802149656

Babiloni, C., Del Percio, C., Iacoboni, M., Infarinato, F., Lizio, R., Marzano, N., et al. (2008). Golf putt outcomes are predicted by sensorimotor cerebral EEG rhythms. *Journal of Physiology, 586,* 131–139. doi:10.1113/jphysiol.2007.141630

Başar, E., & Güntekin, B. (2008). A review of brain oscillations in cognitive disorders and the role of neurotransmitters. *Brain Research, 1235,* 172–193. doi:10.1016/j.brainres.2008.06.103

Bazanova, O. M., & Aftanas, L. I. (2008). Individual measures of electroencephalogram alpha activity and non-verbal creativity. *Neuroscience and Behavioral Physiology, 38*(3), 227–235. doi:10.1007/s11055-008-0034-y

Berger, H. (1929). Über das Elektroenzephalogramm des Menschen. *Archiv für Psychiatrie und Nervenkrankheiten, 1929*(87), 527–557.

Birbaumer, N., Ruiz, S., & Sitaram, R. (2013). Learned regulation of brain metabolism. *Trends in Cognitive Sciences, 17*(6), 295–302. doi:10.1016/j.tics.2013.04.009

Buzsáki, G., Logothetis, N., & Singer, W. (2013). Scaling brain size, keeping timing: evolutionary preservation of brain rhythms. *Neuron, 80*(3), 751–764. doi:10.1016/j.neuron.2013.10.002

Cannon, R., Congedo, M., Lubar, J., & Hutchens, T. (2009). Differentiating a network of executive attention: LORETA neurofeedback in anterior cingulate and dorsolateral prefrontal cortices. *International Journal of Neuroscience, 119,* 404–441.

Cannon, R., Lubar, J., Congedo, M., Thornton, K., Towler, K., & Hutchens, T. (2007). The effects of neurofeedback training in the cognitive division of the cingulate gyrus. *International Journal of Neuroscience, 117,* 337–357.

Cavanagh, J. F., & Frank, M. J. (2014). Frontal theta as a mechanism for cognitive control. *Trends in Cognitive Science, 18*(8), 414–421. doi:10.1016/j.tics.2014.04.012

Cavanagh, J. F., Zambrano-Vazquez, L., & Allen, J. B. (2012). Theta lingua franca: A common mid-frontal substrate for action monitoring processes. *Psychophysiology, 49*(2), 220–238. doi:10.1111/j.1469-8986.2011.01293.x

Cheng, M.-Y., Huang, C.-J., Chang, Y.-K., Koester, D., Schack, T., & Hung, T.-M. (2015). Sensorimotor rhythm neurofeedback enhances golf putting performance. *Journal of Sport & Exercice Psychology, 37*(6), 626–636. doi:10.1123/jsep.2015-0166

Cho, M. K., Jang, H. S., Jeong, S. H., Jang, I. S., Choi, B. J., & Lee, M. G. (2008). Alpha neurofeedback improves the maintaining ability of alpha activity. *NeuroReport, 19*(3), 315–317. doi:10.1097/WNR.0b013e3282f4f022

Cohen, M. X., & Donner, T. H. (2013). Midfrontal conflict-related theta-band power reflects neural oscillations that predict behavior. *Journal of Neurophysiology, 110*(12), 2752–2763. doi:10.1152/jn.00479.2013

Congedo, M., Lubar, J. F., & Joffe, D. (2004). Low resolution electromagnetic tomography neurofeedback. *IEEE Transactions on Neural Systems and Rehabilitation Engineering, 12,* 387–397.

Cooke, A., Kavussanu, M., Gallicchio, G., Willoughby, A., McIntyre, D., & Ring, C. (2014). Preparation for action: Psychophysiological activity preceding a motor skill as a function of expertise, performance outcome, and psychological pressure. *Psychophysiology, 51*(4), 374–384. doi:10.1111/psyp.1218

Donkers, F. C. L., Schwikert, S. R., Evans, A. M., Cleary, K. M., Perkins, D. O., & Belger, A. (2011). Impaired neural synchrony in the theta frequency range in adolescents at familial risk for schizophrenia. *Frontiers in Psychiatry, 22*(2), 55. doi:10.3389/fpsyt.2011.00051

Egner, T., & Gruzelier, J. H. (2004). Ecological validity of neurofeedback: Modulation of slow wave EEG enhances musical performance. *NeuroReport, 14*(9), 1221–1224.

Emmert, K., Kopel, R., Sulzer, J., Brühl, A. B., Berman, B. D., Linden, D. E., …Johnston, S. (2016). Meta-analysis of real-time fMRI neurofeedback studies using individual participant data: How is brain regulation mediated? *NeuroImage 124*, 806–812. doi:10.1016/j.neuroimage.2015.09.042

Engel, A. K., & Singer, W. (2001). Temporal binding and the neural correlates of sensory awareness. *Trends in Cognitive Science, 5*(1), 16–25.

Engelbregt, H. J., Keeser, D., van Eijk, L., Suiker, E. M., Eichhorn, D., Karch, S., et al. (2016). Short and long-term effects of sham-controlled prefrontal EEG-neurofeedback training in healthy subjects. *Clinical Neurophysiology, 172*(4), 1931–1937. doi:10.1016/j.clinph.2016.01.004

Enriquez-Geppert, S., Huster, R. J., Figge, C., & Herrmann, C. S. (2013). Modulation of frontal-midline theta by neurofeedback. *Biological Psychology, 95,* 59–69. doi:10.1016/j.biopsycho.2013.02.019

Enriquez-Geppert, S., Huster, R. J., Figge, C., & Herrmann, C. S. (2014). Self-regulation of frontal-midline theta facilitates memory updating and mental set shifting. *Frontiers in Behavioral Neuroscience, 5*(8), 420. doi:10.3389/fnbeh.2014.00420

Escolano, C., Aquilar, M., & Minguey, J. (2011). EEG-based upper alpha neurofeedback training improves working memory performance. In *Conference Proceedings IEEE Engineering in Medicine and Biology Society* (pp. 2327–2330). doi:10.1109/IEMBS.2011.6090651

Fauth, M., & Tetzlaff, C. (2016). Opposing effects of neuronal activity on structural plasticity. *Frontiers in Neuroanatomy, 10,* 75. doi:10.3389/fnana.2016.00075

Fender, D. H. (1987). Source localization of brain electrical activity. In A. S. Gevins & A. Remond (Eds.), *Handbook of electroencephalography and clinical neurophysiology* (Vol. 1, pp. 355–399). Methods of analysis of brain electrical and magnetic signals. Amsterdam: Elsevier.

Fink, A., & Neubauer, A. C. (2006). EEG alpha oscillations during the performance of verbal creativity tasks: Differential effects of sex and verbal intelligence. *International Journal of Psychophysiology, 62*(1), 46–53.

Ghaziri, J., Tucholka, A., Larue, V., Blanchette-Sylvetre, M., Reyburn, G., Gilbert, G., et al. (2013). Neurofeedback training induces changes in white and gray matter. *Clinical EEG and Neuroscience, 44*(4), 265–272. doi:10.1177/1550059413476031

Grabner, R. H., Fink, A., & Neubauer, A. C. (2007). Brain correlates of self-rated originality of ideas: Evidence from event-related power and phase-locking changes in the EEG. *Behavioral Neuroscience, 121*(1), 224–230.

Gruzelier, J. H. (2014a). EEG-neurofeedback for optimising performance. I. A review of cognitive and affective outcome in healthy participants. *Neuroscience and Biobehavioral Review, 44,* 124–141. doi:10.1016/j.neubiorev.2013.09.015

Gruzelier, J. H. (2014b). EEG-neurofeedback for optimising performance. II. Creativity, the performing arts and ecological validity. *Neuroscience and Biobehavioral Review, 44,* 142–158.

Gruzelier, J. H. (2014c). EEG-neurofeedback for optimising performance. III: A review of methodological and theoretical considerations. *Neuroscience and Biobehavioral Review, 44,* 159–182.

Gruzelier, J. H., Hirst, L., Holmes, P., & Leach, J. (2014a). Immediate effects of alpha-theta and sensory/motor rhythm feedback on music performance. *International Journal of Psychophysiology, 93*(1), 96–106. doi:10.1016/j.ijpsycho.2014.03.009

Gruzelier, J. H., Thompson, T., Redding, E., Brandt, R., & Steffert, R. (2014b). Application of Alpha-theta neurofeedback and heart rate variability training to young contemporary dancers: State anxiety and creativity. *International Journal of Psychophysiology, 93*(1), 105–111. doi:10.1016/j.neubiorev.2013.11.004

Guez, J., Rogel, A., Getter, N., Keha, E., Cohen, T., Amor, T., et al. (2014). Influence of electroencephalography neurofeedback training on episodic memory: A randomized, sham-controlled, double-blind study. *Memory, 23*(5), 683–694. doi:10.1080/09658211.2014.921713

Hanslmayr, S., Sauseng, P., Doppelmayr, M., Schabus, M., & Klimesch, W. (2005). Increasing individual upper alpha power by neurofeedback improves cognitive performance in human subjects. *Applied Psychophysiology and Biofeedback., 30*(1), 1–10.

Hardman, E., Gruzelier, J., Cheesman, K., Jones, C., Liddiard, D., Schleichert, H., et al. (1997). Frontal interhemispheric asymmetry: Self-regulation and individual differences in humans. *Neuroscience Letters, 221*(2), 117–120. doi:10.1016/S0304-3940(96)13303-6

Herrmann, C. S., & Knight, R. T. (2001). Mechanisms of human attention: Event-related potentials and oscillations. *Neuroscience and Biobehavioral Review, 25*(6), 465–476. doi:10.1016/S0149-7634(01)00027-6

Hoedlmoser, K., Pecherstorfer, T., Gruber, G., Anderer, P., Doppelmayr, M., Klimesch, W., et al. (2008). Instrumental conditioning of human sensorimotor rhythms (12–15 Hz) and its impact on sleep as well as declarative learning. *Sleep, 31*(19), 1401–1408. doi:10.1016/j.ijpsycho.2012.07.182

Horschig, J. M., Jensen, O., van Schouwenburg, M. R., Cools, R., & Bonnefond, M. (2014). Alpha activity reflects individual abilities to adapt to the environment. *NeuroImage, 89,* 235–243. doi:10.1016/j.neuroimage.2013.12.018

Hsueh, J.-J., Chen, T.-S., Chen, J.-J., & Shaw, F.-Z. (2016). Neurofeedback training of EEG alpha rhythm enhances episodic and working memory. *Human Brain Mapping, 37*(7), 2662–2675.

Hulme, S. R., Jones, O. D., & Abraham, W. C. (2013). Emerging roles of metaplasticity in behaviour and disease. *Trends in Neurosciences, 36*(6), 353–362. doi:10.1016/j.tins.2013.03.007

Huster, R. J., Mokom, Z. N., Enriquez-Geppert, S., & Herrmann, C. S. (2014). Brain–computer interfaces for EEG neurofeedback: Peculiarities and solutions. *International Journal Psychophysiology., 91*(1), 36–45. doi:10.1016/j.ijpsycho.2013.08.011

Ishihara, T., Hayashi, H., & Hishikawa, Y. (1981). Distribution of frontal midline theta rhythm (Fm0) on the scalp in different states (mental calculation, resting and drowsiness). *Electroencephalography and Clinical Neurophysiology, 52*(3), 19. doi:10.1016/0013-4694(81)92408-1

Janssen, T. W., Bink, M., Gelade, K., van Mourik, R., Maras, A., & Oosterlaan, J. (2016). A randomized controlled trial into the effects of neurofeedback, methylphenidate, and physical activity on EEG power spectra in children with ADHD. *Journal of Child Psychology and Psychiatry, 57*(5), 633–644. doi:10.1111/jcpp.12517

Kamiya, J. (2011). The first communications about operant conditioning of the EEG. *Journal of Neurotherapy, 15*(1), 65–73.

Keizer, A. W., Verment, R. S., & Hommel, B. (2010a). Enhancing cognitive control through neurofeedback: A role of gamma-band activity in managing episodic retrieval. *NeuroImage, 49*(4), 3404–3413. doi:10.1016/j.neuroimage.2009.11.023

Keizer, A., Verschoor, M., Verment, R. S., & Hommel, B. (2010b). The effect of gamma enhancing neurofeedback on the control of feature bindings and intelligence measures. *International Journal Psychophysiology., 75*(19), 25–32. doi:10.1016/j.ijpsycho.2009.10.011

Kikkert, A. (2015). *Predictors of neurofeedback efficacy: An exploratory study to the influence of personality and cognitive characteristics on the efficacy of theta and beta neurofeedback training*. Dissertation, University of Leiden.

Klimesch, W. (1999). EEG alpha and theta oscillations reflect cognitive and memory performance: A review and analysis. *Brain Research Review, 29*(2–3), 169–195. doi:10.1016/S0165-0173(98)00056-3

Kluetsch, R. C., Ros, R., Theberge, J., Frewen, P. A., Calhoun, V. D., Schmach, C., et al. (2014). Plastic modulation of PTSD resting-state networks and subjective wellbeing by EEG neurofeedback. *Acta Psychiatrica Scandinavica, 130*(2), 123–136. doi:10.1111/acps.12229

Knoblauch, A., Hauser, F., Gewaltig, M.-O., Körner, E., & Palm, G. (2012). Does spike-timing-dependent synaptic plasticity couple or decouple neurons firing in synchrony? *Frontiers in Computational Neuroscience, 6,* 55. doi:10.3389/fncom.2012.00055

Kober, S. E., Schweiger, D., Witte, M., Reichert, J. L., Grieshofer, P., Neuper, C., et al. (2015a). Specific effects of EEG based neurofeedback training on memory functions in post-stroke victims. *Journal Neuroengineering and Rehabilitation, 12*(1), 1. doi:10.1186/s12984-015-0105-6

Kober, S. E., Witte, M., Ninaus, M., Koschutnig, K., Neuper, C., & Wood, G. (2015b). *Spirituality and the ability to gain control over one's own brain activity: A multimodal imaging study*. Geneva: Organization for Human Brain Mapping.

Kober, S. E., Witte, M., Ninaus, M., Neuper, C., & Wood, G. (2013). Learning to modulate one's own brain activity: The effect of spontaneous mental strategies. *Frontiers in Human Neuroscience, 7,* 695. doi:10.3389/fnhum.2013.00695

Kober, S. E., Witte, M., Stangl, M., Väljamäe, A., Neuper, C., & Wood, G. (2015c). Shutting down sensorimotor interference unblocks the networks for stimulus processing: An SMR neurofeedback training study. *Clinical Neurophysiology, 126*(1), 82–95. doi:10.1016/j.clinph.2014.03.031

Legenstein, R., Pecevski, D., & Maass, W. (2008). A learning theory for reward-modulated spike-timing-dependent plasticity with application to biofeedback. *PLoS Computational Biology, 4*(10), e1000180. doi:10.1371/journal.pcbi.1000180

Lévesque, J., Beauregard, M., & Mensour, B. (2006). Effect of neurofeedback training on the neural substrates of selective attention in children with attention-deficit/hyperactivity disorder: A functional magnetic resonance imaging study. *Neuroscience Letters, 394*(3), 216–221.

Lubar, J. F., & Swartwood, M. (1995). Quantitative EEG and auditory event-related potentials in the evaluation of attention-deficit/hyperactivity disorder: Effects of methylphenidate and implications for neurofeedback training. *Journal of Psychoeducational Assessment, 1938,* 143–160.

Maurizio, S., Liechti, M. D., Heinrich, H., Jäncke, L., Steinhausen, H. C., Walitza, S., et al. (2014). Comparing tomographic EEG neurofeedback and EMG biofeedback in children with attention-deficit/hyperactivity disorder. *Biological Psychology, 95,* 31–44.

Mitchell, D. J., McNaughton, N., Flanagan, D., & Kirk, I. J. (2008). Frontal-midline theta from the perspective of hippocampal "theta". *Progress in Neurobiology, 86*(3), 156–185. doi:10.1016/j.pneurobio.2008.09.005

Monastra, V. J., Monastra, D. M., & George, S. (2002). The effects of stimulant therapy, EEG biofeedback, and parenting style on the primary symptoms of attention-deficit/hyperactivity disorder. *Applied Psychophysiology and Biofeedback, 27*(4), 231–249.

Musall, S., Von Pföstl, V., Rauch, A., Logothetis, N. K., & Whittingstall, K. (2014). Effects of neural synchrony on surface EEG. *Cerebral Cortex, 24*(4), 1045–1053. doi:10.1093/cercor/bhs389

Nan, W., Rodrigues, J. R., Ma, J., Qu, X., Wan, F., Mak, R.-I., et al. (2012). Individual alpha neurofeedback training effect on short term memory. *International Journal Psychophysiology, 86*(1), 83–87. doi:10.1016/j.ijpsycho.2012.07.182

Niendam, T. A., Lair, A. R., Kimberly, L. R., Dean, Y. M., & Carter, C. S. (2012). Meta-analytic evidence for a superordinate cognitive control network subserving diverse executive functions.

Cognitive Affective and Behavioral Neuroscience, 12(2), 241–268. doi:10.3758/s13415-011-0083-5

Ninaus, M., Kober, S. E., Witte, M., Koschutnig, K., Neuper, C., & Wood, G. (2015). Brain volumetry and self-regulation of brain activity relevant for neurofeedback. *Biological Psychology, 110,* 126–133. doi:10.1016/j.biopsycho.2015.07.009

Ninaus, M., Kober, S. E., Witte, M., Koschutnig, K., Stangl, M., Neuper, C., et al. (2013). Neural substrates of cognitive control under the belief of getting neurofeedback training. *Frontiers in Human Neuroscience, 7,* 914. doi:10.3389/fnhum.2013.00914

Okazaki, Y. O., Horschig, J. M., Luther, L., Oostenveld, R., Murakami, I., & Jensen, O. (2015). Real-time MEG neurofeedback training of posterior alpha activity modulates subsequent visual detection performance. *NeuroImage, 107,* 323–332. doi:10.1016/j.neuroimage.2014.12.014

Pascual-Marqui, R. D., Michel, C. M., & Lehmann, D. (1994). Low-resolution electromagnetic tomography—a new method for localizing electrical-activity in the brain. *International Journal Psychophysiology, 18*(1), 49–65. doi:10.1016/0167-8760(84)90014-X

Pfister, J.-P., & Tass, P. A. (2010). STDP in oscillatory recurrent networks: Theoretical conditions for desynchronization and applications to deep brain stimulation. *Frontiers in Computational Neuroscience, 4*(July), 1–10. doi:10.3389/fncom.2010.00022

Raymond, J., Sajid, I., Parkinson, L. A., & Gruzelier, J. H. (2005). Biofeedback and dance performance: A preliminary investigation. *Applied Psychophysiology and Biofeedback, 30*(1), 64–73.

Regestein, Q. R., Pegram, G. V., Cook, B., & Bradley, D. (1973). Alpha rhythm percentage maintained during 4- and 12-hour feedback periods. *Psychosomatic Medicine, 35*(3), 215–222.

Reichert, J. L., Kober, S. E., Neuper, C., & Wood, G. (2016a). Resting-state sensorimotor rhythm (SMR) power predicts the ability to up-regulate SMR in an EEG-instrumental conditioning paradigm. *Clinical Neurophysiology, 126*(11), 2068–2077. doi:10.1016/j.clinph.2014.09.032

Reichert, J. L., Kober, S. E., Schweiger, D., Grieshofer, P., Neuper, C., & Wood, G. (2016b). Shutting down sensorimotor interferences after stroke: A proof-of-principle SMR neurofeedback study. *Frontiers in Human Neuroscience*. doi:10.3389/fnhum.2016.00348

Reichert, J. L., Kober, S. E., Witte, M., Neuper, C., & Wood, G. (2016c). Age-related effects on verbal and visuospatial memory are mediated by theta and alpha II rhythms. *International Journal Psychophysiology., 99,* 67–78.

Rice, J. K., Rorden, C., Little, J. S., & Parra, L. C. (2013). Subject position affects EEG magnitudes. *NeuroImage, 64,* 476–484.

Rihs, T. A., Michel, C. M., & Thut, G. (2007). Mechanisms of selective inhibition in visual spatial attention are indexed by alpha-band EEG synchronization. *European Journal of Neuroscience, 25*(2), 603–610.

Ring, C., Cooke, A., Kavussnu, M., McIntyre, D., & Masters, R. (2015). Investigating the efficacy of neurofeedback training for expediting expertise and excellence in sport. *Psychology of Sport and Exercise, 16*(1), 118–127. doi:10.1016/j.psychsport.2014.08.005

Rogala, J., Ruewicz, J., Paluch, K., Kublik, E., Cetnarski, R., & Wrobel, A. (2016). The do's and don'ts of neurofeedback training: A review of the controlled studies using healthy adults. *Frontiers in Human Neuroscience*. doi:10.3389/fnhum.2016.00301 (eCollection 2016).

Ros, T. J., Baars, B., Lanius, R. A., & Vuilleumier, P. (2014). Tuning pathological brain oscillations with neurofeedback: A systems neuroscience framework. *Frontiers in Human Neuroscience, 8,* 1008. doi:10.1016/j.ijpsycho.2015.11.004

Ros, T., Frewen, P., Theberge, J., Michela, A., Kluetsch, R., Mueller, M., et al. (2016). Neurofeedback tunes scale-free dynamics in spontaneous brain activity. *Cerebral Cortex*. doi:10.1093/cercor/bhw285

Ros, T., Moseley, M. R., Bloom, P. A., Benjamin, L., Parkinson, L. A., & Gruzelier, J. H. (2009). Optimizing microsurgical skills with EEG neurofeedback. *BMC Neuroscience, 10,* 87. doi:10.1186/1471-2202-10-8

Ros, T., Munneke, M., Ruge, D., Gruzelier, J., & Rothwell, J. (2010). Endogenous control of waking brain rhythms induces neuroplasticity in humans. *European Journal of Neuroscience, 31*(4), 770–778. doi:10.1111/j.1460-9568.2010.07100.x

Ros, T., Theberge, J., Frewen, P. A., Gluetsch, R., Densmore, M., Calhoun, V. D., et al. (2013). Mind over chatter: Plastic up-regulation of the fMRI salience network directly after EEG neurofeedback. *NeuroImage, 65,* 324–335. doi:10.1016/j.neuroimage.2012.09.046

Salari, N., Buchel, C., & Rose, M. (2013). Functional dissociation of ongoing oscillatory brain states. *PLoS ONE, 7,* e38090.

Sauseng, P., & Klimesch, W. (2008). What does phase information of oscillatory brain activity tell us about cognitive processes? *Neuroscience and Biobehavioral Review, 32*(5), 1001–1013.

Schabus, M., Heib, D. P. J., Lechinger, J., Griessenberger, H., Klimesch, W., Pawlizki, A., et al. (2014). Enhancing sleep quality and memory in insomnia using instrumental sensorimotor rhythm conditioning. *Biological Psychology, 95,* 126–134.

Schachter, D. L. (1976). The hypnagogic state: A critical review of the literature. *Psychological Bulletin, 83*(3), 452–481.

Schulz, P. E., & Fitzgibbons, J. C. (1997). Differing mechanisms of expression for short- and long-term potentiation. *Journal of Neurophysiology, 78*(1), 321–334.

Sederberg, P. B., Kahana, M. J., Howard, M. W., Donner, E. J., & Madsen, J. R. (2003). Theta and gamma oscillations during encoding predict subsequent recall. *Journal of Neuroscience, 23*(34), 10809–10814.

Sittenfeld, P., Budzynski, T., & Stoyva, J. (1976). Differential shaping of EEG theta rhythms. *Biofeedback and Self Regulation, 1*(1), 31–46.

Sporns, O. (2014). Contributions and challenges for network models in cognitive neuroscience. *Nature Neuroscience, 17*(5), 652–660.

Staufenbiel, S. M., Brouwer, A. M., Keizer, A. W., & van Wouwe, N. C. (2014). Effect of beta and gamma neurofeedback on memory and intelligence in the elderly. *Biological Psychology, 95,* 74–85. doi:10.1016/j.biopsycho.2013.05.020

Steriade, M. (1999). Coherent oscillations and short-term plasticity in corticothalamic networks. *Trends in Neuroscience, 22*(8), 337–345.

Sterman, M. B., Howe, R. C., & MacDonald, L. R. (1970). Facilitation of spindle burst sleep by conditioning of electroencephalographic activity while awake. *Science, 167,* 1146–1148.

Sterman, M. B., Wyrwicka, W., & Howe, R. (1969). Behavioral and neurophysiological studies of the sensorimotor rhythm in the cat. *Electroencephalogramm and Clinical Neurophysiology, 27,* 678–679.

Tallon-Baudry, C., & Bertrand, O. (1999). Oscillatory gamma activity in humans and its role in object representation. *Trends in Cognitive Science., 3*(4), 151–162.

Tass, P. A., Silchenko, A. N., Hauptmann, C., Barnikol, U. B., & Speckmann, E. J. (2009). Long-lasting desynchronization in rat hippocampal slice induced by coordinated reset stimulation. *Physical Review E, 80*(1 Pt 1), 011902.

Thut, G., Nietzel, A., Brandt, S. A., & Pascual-Leone, A. (2006). Alpha-band electroencephalographic activity over occipital cortex indexes visuospatial attention bias and predicts visual target detection. *Journal of Neuroscience, 26*(37), 9494–9502.

van Gerven, M., & Jensen, O. (2009). Attention modulations of posterior alpha as a control signal for two-dimensional brain–computer interfaces. *Journal of Neuroscience and Methods., 179* (1), 78–84. doi:10.1016/j.jneumeth.2009.01.016

van Lutterveld, R., Houlihan, S. D., Pal, P., Cacchet, M. D., McFarlane-Blake, C., Sullivan, J. S., Ossadtchi, A., Druker, S., Cauer, C., & Brewer, J. A. (2016). Source-space EEG neurofeedback links subjective experience with brain activity during effortless awareness meditation. *NeuroImage*. doi:10.1016/j.neuroimage.2016.02.047 (Epub ahead of print).

Vernon, D., Egner, T., Cooper, N., Compton, T., Neilands, C., Sheri, A., et al. (2003). The effect of training distinct neurofeedback protocols on aspects of cognitive performance. *International Journal Psychophysiology., 47*(1), 75–85. doi:10.1016/S0167-8760(02)00091-0

Vossen, A., Gross, J., & Thut, G. (2015). Alpha power increase after transcranial alternating current stimulation at alpha frequency (α-tACS) reflects plastic changes rather than entrainment. *Brain Stimulation., 8*(3), 499–508. doi:10.1016/j.brs.2014.12.004

Wang, J.-R., & Hsieh, S. (2014). Neurofeedback training improves attention and working memory performance. *Clinical Neurophysiology, 142*(1), 2406–2420. doi:10.1016/j.clinph.2013.05.020

Whitt, J. L., Petrus, E., & Lee, H. K. (2013). Experience-dependent homeostatic synaptic plasticity in neocortex. *Neuropharmacology, 78,* 45–54. doi:10.1016/j.neuropharm.2013.02.016

Witte, M. (2015). With body and soul—A comparison of self-regulatory mechanisms required for neurofeedback in triathletes and healthy controls. In *OHBM Alpine chapter symposium and 15th Austrian fMRI symposium*, Wien, 27 November 2015.

Witte, M., Kober, S. E., Ninaus, M., Neuper, C., & Wood, G. (2013). Control beliefs can predict the ability to up-regulate sensorimotor rhythm during neurofeedback training. *Frontiers in Human Neuroscience., 7,* 478. doi:10.3389/fnhum.2013.00478

Wood, G., Kober, S. E., Witte, M., & Neuper, C. (2014). On the need to better specify the concept of "control" in brain–computer-interfaces/neurofeedback research. *Frontiers in Systems Neuroscience., 8,* 171. doi:10.3389/fnsys.2014.00171

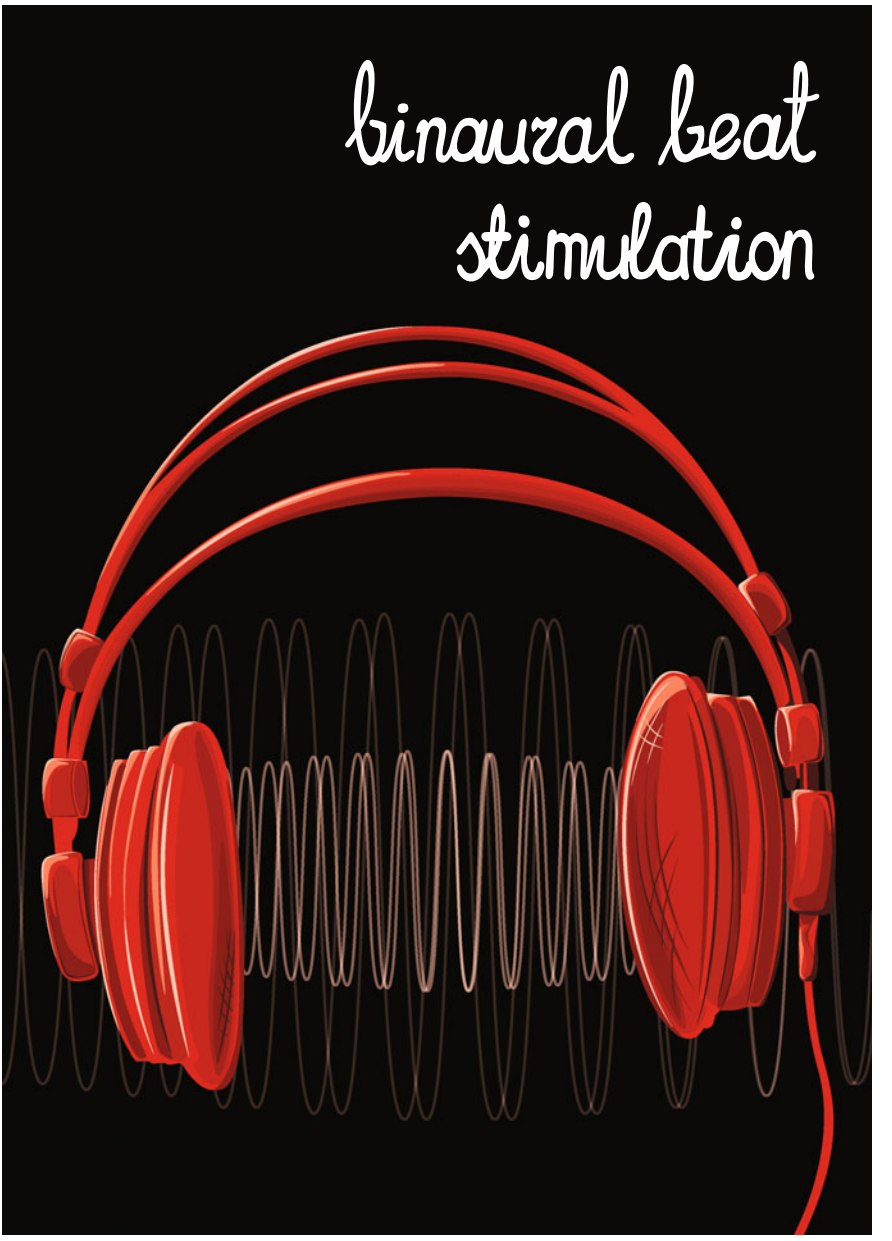
Enriquez-Geppert, S., Huster, R. J., & Herrmann, C. S. (subm.). *EEG-neurofeedback as a tool to modulate brain oscillations: A review tutorial*.

Zaehle, T., Rach, S., & Herrmann, C. S. (2010). Transcranial alternating current stimulation enhances individual alpha activity in human EEG. *PLoS ONE, 5*(11), e13766. doi:10.1371/journal.pone.0013766

Zoefel, B., Huster, R. J., & Herrmann, C. S. (2010). Neurofeedback training of the upper alpha frequency band in EEG improves cognitive performance. *NeuroImage., 54*(2), 1427–1431. doi:10.1016/j.neuroimage.2010.08.078

Zotev, V., Krueger, F., Phillipps, R., Alvarez, R. P., Simmons, R. K., Bellgowan, P., et al. (2011). Self-regulation of amygdala activation using real-time fMRI neurofeedback. *PLoS ONE, 6,* e24522.

Zotev, V., Phillips, R., Yuan, H., Misaki, M., & Bodurka, J. (2014). Self-regulation of human brain activity using simultaneous real-time fMRI and EEG neurofeedback. *NeuroImage, 85,* 985–995.


binaural beat
stimulation

Binaural Beat Stimulation

Leila Chaieb and Juergen Fell

Introduction

Over the last 20 years, binaural beat stimulation has been investigated as a potential tool for neuro-enhancement or as an alternative therapeutic measure with which to alter mood states and reduce levels of anxiety. Here, we aim to give an up-to-date overview of the current state of research on binaural beats and to highlight promising new avenues of investigation. Although many studies report weak and short-lived effects of binaural beats, there is evidence to suggest a role for this kind of stimulation in modulating cognition. Recent research examining the effects of monaural and binaural beats on phase synchronization suggests potential mechanisms underlying the modulation of memory processes and attention. Binaural beat stimulation has been shown to modulate vigilance, as measured by task performance, as well as creativity and problem solving in a divergent thinking task. Taken together, these studies demonstrate a level of interaction between binaural beat stimulation and the brain. However, many studies using similar approaches often report contrasting findings. In this chapter, we try to understand why these discrepancies in the research occur. With optimized stimulation protocols, binaural beats may offer a safe and reliable method of modulating mood states and reducing anxiety-related symptoms.

L. Chaieb (✉) · J. Fell
Department of Epileptology, University of Bonn, Sigmund-Freud Str. 25,
53105 Bonn, Germany
e-mail: Leila.Chaieb@ukb.uni-bonn.de

L.S. Colzato, *Theory-Driven Approaches to Cognitive Enhancement*,
DOI 10.1007/978-3-319-57505-6_12

Auditory Beat Stimulation (ABS) Comprises Monaural and Binaural Beats

Auditory beat stimulation is the application of monaural and binaural beat stimuli in order to alter or modulate physiological or cognitive processes. These beat stimuli are generated in different ways, which give rise to characteristics distinguishing these two different kinds of beats from one another. Monaural beats are physical, acoustic beats which are heard when two sine waves of nearby frequencies, and with stable amplitudes are presented to both ears simultaneously. For example, when two sine waves of 100 and 120 Hz are presented to both ears at the same time, the waves are summated and result in an amplitude modulated signal. The frequency of the monaural beat generated by the two summated waves corresponds to the frequency difference between the two sine waves, which in this example is 20 Hz. Binaural beats, however, are generated when two sine waves of neighbouring frequencies are presented to each ear separately. Following on from the previous example, when a sine wave of 100 Hz is presented to the left ear and a 120 Hz tone to the right ear, a subjective beat of 20 Hz is perceived (see Fig. 1 for an overview of how monaural and binaural beats are generated). This auditory illusion is called the binaural beat percept and was first reported by H.W. Dove in 1839. Binaural beats require the combined involvement of both ears in order to perceive them, whereas monaural beats can be sufficiently heard with just one ear. Over 100 years later, Oster reported comprehensively on what he termed the binaural beat 'phenomenon' and observed that binaural beats can be perceived only when the base carrier tones used to produce them are of sufficiently low pitch (Oster 1973). In this case lower than 1000 Hz, an observation by an earlier study later confirmed (Licklider et al. 1950).

Monaural and Binaural Beats are Processed Differently in the Brain

The differences between how monaural and binaural beats are generated are underlined by the neurophysiological processing of these two different kinds of tones. As a result, they are often referred to as either 'peripheral' in the case of monaural beats or 'central', for binaural beats (Draganova et al. 2008).

In general, acoustic beats are detected by the ears and then relayed via the vestibulocochlear nerve after leaving the cochlear, where inner hair cells convert sound pressure waves through mechano-electrical transduction into action potentials. These action potentials are then eventually encoded in the primary auditory cortex. Information leaving the cochlear is transmitted to either the inferior colliculus (IC) or the superior olivary complex (SOC) by subgroups of nuclei comprising the cochlear nucleus. Outputs from the IC and SOC arrive in the medial geniculate nucleus (MGN) of the thalamus and project output fibres which connect

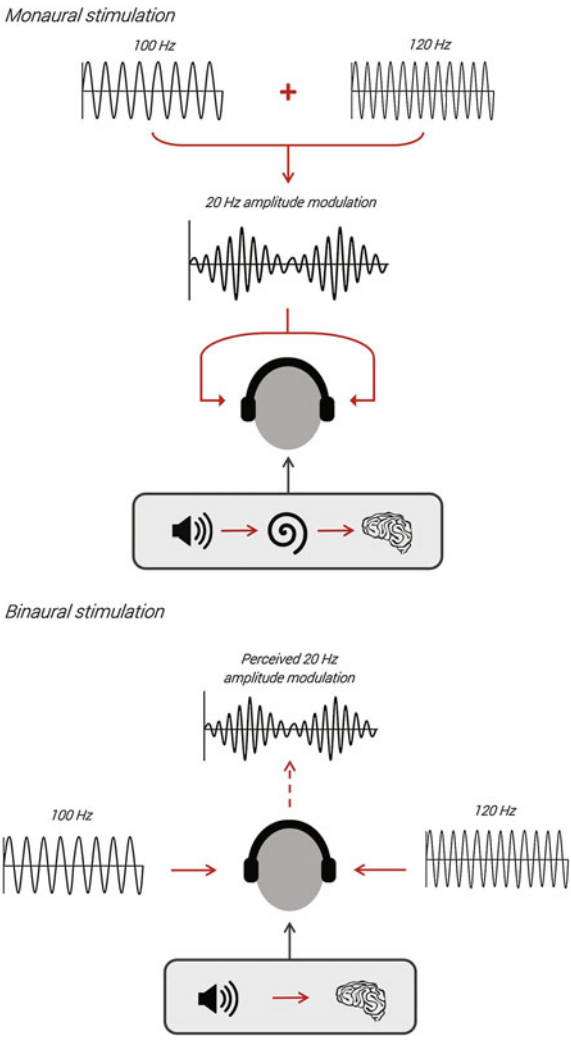


Fig. 1 Overview of the concept of monaural and binaural beats. Monaural beats are heard when sine waves of neighbouring frequencies are presented to either one ear or both ears simultaneously. Binaural beats are perceived when the same superimposed amplitude modulated signals are delivered to each ear separately. In this example, carrier tones of 100 and 120 Hz produce 20 Hz monaural and binaural beats

to the auditory cortex in the temporal lobes (for a comprehensive review on sound processing see: Squire et al. 2008; Schnupp et al. 2012).

Monaural beats interact peripherally at the level of the cochlear, where sound information is relayed to the brainstem, IC and processed in the auditory cortex. Binaural beats, however, are perceived as a result of a central interaction in the superior olivary nuclei (Draganova et al. 2008). Brainstem neurons in the SOC which are sensitive to intra-aural phase shifts fire action potentials at a rate which corresponds to the phase difference between both ears. This interaction generates that binaural beat percept. The neural mechanism responsible for sound localization is the same as that which generates the binaural beat percept (Kuwada et al. 1979).

Cortical Responses to Monaural and Binaural Beats

Many studies have aimed to localize the origin of monaural and binaural beat frequencies by examining the auditory-steady-state response (ASSR) to these tones. This has been subject of much debate (Pantev et al. 1996; Karino et al. 2006; Draganova et al. 2008). The ASSR is a composite auditory evoked potential which can be elicited using repetitive acoustic stimuli which continually persist over a time period (Picton et al. 2003). For example, Galambos et al. recorded event-related potentials (ERPs) to click stimuli, with latencies between 8 and 80 ms after the onset of the click stimulus. The ERP was most detectable when the click stimuli were delivered at 40 stimuli per second, giving rise to the subsequently termed 40 Hz ERP (Galambos et al. 1981).

The ASSR has since become a useful tool in identifying the source of binaural beat frequencies in the brain. In a magnetoencephalography (MEG) study, ASSRs recorded using binaural beat frequencies of 4.00–6.66 Hz showed that the binaural beat ASSR was most prominent at the superior temporal, posterior parietal and frontal cortices, as well as the primary auditory cortex (Karino et al. 2006). A similar study also using MEG found the source of both the monaural and binaural ASSRs to be located anterior and medial to Heschl's gyri within the Sylvian fissure. One of these studies placed the ASSR generating network within the primary auditory cortex, a finding confirmed by earlier studies (Draganova et al. 2002; Ross et al. 2003).

There are differences between the ASSR elicited from monaural beats compared to those for binaural beats. Draganova et al. (2008) reported that the magnetic field amplitudes of the ASSR generated using monaural beat stimuli were around 5 rules greater than those of the binaural beats at the same frequency (Draganova et al. 2008). Schwarz and Taylor (2005) also observed that the ASSR evoked amplitude response to 40 Hz monaural beats was larger than that of the binaural beat ASSR. The binaural beat ASSR was elicited using a carrier frequency of 400 Hz, but was rendered undetectable using carrier frequencies above 3000 Hz. The authors reported that this was not the case for the monaural beat stimuli which continued to be detected above 3000 Hz (Schwarz and Taylor 2005). Two studies comparing ERP responses to binaural and monaural beat stimuli also showed similar effects on the response amplitudes of the ERPs recorded using surface EEG. The authors reported that ERPs evoked during monaural and binaural beat stimulation were larger when carrier frequencies were lower (250 Hz compared to 1000 Hz) and when the beat stimulation frequency itself was lower (3 Hz as opposed to 6 Hz) (Pratt et al. 2009, 2010). Pratt et al. (2010) also observed that the sources of the ERPs to both monaural and binaural beat stimuli were in the temporal lobes regions and lateralized to the left hemisphere (Pratt et al. 2010). In summary, the findings of these studies suggest that binaural and monaural beats are processed in the same cortical regions and cortical responses recorded using these beats are affected by both the stimulating frequency and base carrier frequencies.

Binaural Beat Stimulation Exerts Transient Effects on EEG

A few studies have sought to examine the effects of auditory beat stimulation on frequency bands by recording continuous EEG. These changes have mainly been detected in the alpha (Vernon et al. 2012) and gamma (Schwarz and Taylor 2005) range. In a study applying binaural beat stimulation in the alpha (10 Hz) and beta (20 Hz) frequency ranges, a slight decrease in resting baseline amplitudes for both beat frequencies, when pre- and post-stimulation trials were compared, was observed. EEG was recorded from the left and right temporal regions while the beat frequencies at 10 Hz (alpha) and 20 Hz (beta) were played for 1 min over a total of 10 trials. Each trial was followed by exposure to a 400 Hz pure tone, used as a control measure. However, the authors reported that overall there was no significant effect of beat stimulation frequencies on the EEG (Vernon et al. 2012). Using a similar approach, Gao et al. (2014) examined the effects of binaural beats applied for 5 min, at 1, 5, 10 and 20 Hz. They analysed relative power (RP), phase locking values (PLVs) and cross-mutual information (CMI) to detect changes in the EEG. In theta and alpha bands, relative power increased during delta and alpha beat stimulation, but decreased in the beta band. A reduction in CMI was observed in right temporal, frontal and occipital areas 3.5 min after stimulation onset, during alpha and delta beat stimulation. Interestingly, the authors detected an initial increase and then subsequent decrease in CMI during beta binaural beat stimulation, which occurred between the left temporal and frontal areas (an increase), and between right temporal and centro-parietal areas (a decrease). For theta beat stimulation, an increase over the left temporal and central areas was seen. These findings suggest that application of binaural beats in a wider range of frequency bands (theta, alpha, delta and beta) is able to alter functional connectivity between brain regions (Gao et al. 2014).

Other studies have aimed to identify whether certain beat stimulation frequencies can either have diminishing or enhancing effects on cortical responses. Lavallee et al. (2011) reported that binaural beat frequencies at 7 and 15 Hz were able to induce entrainment effects during a study looking at the effects of binaural beats on meditation practices. Theta (7 Hz) frequency beat stimulation increased left temporal lobe delta power in experienced meditators but not in novice practitioners. Beta (15 Hz) frequency stimulation increased gamma power in novice meditators, but this effect was not seen in the experienced group (Lavallee et al. 2011). These findings suggest that the effects of binaural beat stimulation may depend upon the experience and skill set of the individual. As more research emerges examining the effects of auditory beat stimulation, the impact of inter-individual differences may become more important. One of the first studies to highlight the relevance of this effect showed that high-frequency binaural beats (40 Hz) modulated attentional control in an attentional blink task, but only in individuals with low striatal dopamine levels, measured using spontaneous eye blink rates (Reedijk et al. 2013). This study underlines the notion that neuro-enhancement techniques often seem ineffective, when protocols addressing inter-individual differences may be more suitable.

Mechanism of Action: Monaural and Binaural Beats May Influence Cognition Through Phase Synchronization

Phase synchronization is integral to cognition as it supports the processes of neural communication, neuroplasticity and memory formation (Fell and Axmacher 2011). It occurs when oscillations in two brain regions have a constant phase over a time period. Data recorded via intracranial EEG in presurgical epilepsy patients suggest that monaural and binaural beats are able not only to alter EEG power, but also phase synchronization. Becher et al. (2014) reported, for instance, an increase in temporo-lateral phase synchronization due to 5 Hz binaural beat stimulation. Monaural beats at the same frequency decreased mediotemporal synchronization (Becher et al. 2014). In an earlier study, Schwarz and Taylor (2005) examined monaural and binaural beats ASSRs derived from scalp EEG recordings at different electrode locations. They observed a fronto-occipital phase shift in both binaural and monaural beat ASSRs, elicited at 40 Hz. The phase shifts had a lag of ~3–7 ms, and indicated that the monaural and binaural beat ASSRs are generated by more than one neuronal network at different locations. The authors suggest that the data either could have been generated by more than one source with different orientations, or the rostro-caudal phase shift of gamma oscillations may be due to recruitment of several cortical regions (Schwarz and Taylor 2005). In a recent study, bilateral phase differences for binaural beats could be detected, while evoked responses to monaural beats showed equal phase in both the left and right hemispheres (Ross et al. 2014). The phase delays observed by both Schwarz and Taylor (2005) and Ross et al. (2014) may also indicate changes in phase synchronization. If auditory beats do indeed modify phase synchronization, this may suggest a role for monaural and binaural beats in modulating memory processes.

Binaural Beat Stimulation and Cognition

Stimulation methods that are able to enhance cognitive processes or modulate mood states or pain responses continue to be the subject of much debate. Studies show that auditory beat stimulation may be a promising new tool with which to manipulate cognition, as it is easy to apply and the after effects of the stimulation are reversible. Here, we will summarize studies that have reported effects of beat stimulation on cognitive processes.

The Impact of Binaural Beats on Attention

A study examined the potential therapeutic application of binaural beats on reducing inattention in a cohort of children and adolescents diagnosed with attention-deficit/hyperactivity disorder (ADHD). ADHD is a neuropsychiatric

disorder that affects children and adolescents. It is characterized by the core symptoms of inattention, impulsivity and hyperactivity which can be seen over a spectrum of severity (Barkley 2005). Binaural beats were administered to participants three times per week for 20 min each session, continually for three weeks. The participants were required to listen to a commercially prepared audio program with binaural beats embedded within natural sounds or a sham recording containing pink noise. The exact parameters of the binaural beat stimulation, however, were not reported. Changes in attention were measured using the Test of Variables of Attention (TOVA), as well as implementing the Children's Colour Trails Test version 1 and 2 (CCTT1 and 2). Kennel et al. (2010) reported no significant changes in attention measures, however, the participants themselves reported subjectively less problems associated with inattention during the treatment period.

In two recent studies, the effects of high-frequency binaural beats on attentional processes have been investigated. Reedijk et al. (2015) used the attentional blink (AB) task, where participants must attend to two targets which are presented in rapid succession. During the AB task, participants are able to respond to the first target but often miss the second if it appears in an early time window after presentation of the first target (Raymond et al. 1992). The task measures the attentional resources allocated between the targets. The AB task is subject to an individual's bias towards either the frontal dopaminergic pathway or the striatal dopaminergic pathway (Cools 2008). Bias towards the striatal pathway is correlated with higher spontaneous eye-blink rates (EBRs) (Dreisbach et al. 2005; Colzato et al. 2010). Over three sessions, participants listened to alpha (10 Hz), gamma (40 Hz) binaural beats or a control tone (340 Hz), for 3 min before and during task execution. EBRs were measured prior to each session for 5 min. Using the AB task and EBRs, Reedijk et al. (2015) reported that 40 Hz binaural beat stimulation abolished the AB effect in individuals with a low EBR. The authors suggested that presenting high-frequency binaural beats to participants with a low EBR may boost activity in the gamma band through entrainment of oscillations during the presentation of targets in the AB task (Reedijk et al. 2015). More importantly, this study highlights the case for improving the outcomes of stimulation protocols by selective or 'tailored' (Reedijk et al. 2015) stimulation parameters based on the individual.

In a second study, Colzato et al. (2015) showed that high-frequency binaural beats (40 Hz) are able to increase attentional focusing towards a reduced spotlight of attention, compared to a control tone (340 Hz) using the global–local task. The global–local task measures the speed at which participants are able to process global versus local features of visual stimuli. Participants were given either gamma frequency binaural beats or a 340 Hz control tone in two sessions, for 3 min prior to and during the task. The authors reported that 40 Hz binaural beat stimulation did not affect the participant's ability to suppress task-irrelevant information. The global precedence effect (a measure of bias towards processing local information) was significantly reduced after exposure to 40 Hz beat stimulation. Taken together, these studies suggest a role for binaural beat stimulation in modulating selective attention and related attentional processes.

Effects of Binaural Beats on Creativity

A study investigating the effect of alpha (10 Hz) and gamma (40 Hz) binaural beats on creativity demonstrated a difference between the effect of beat stimulation on divergent versus convergent thinking strategies (Reedijk et al. 2013). It is understood that creativity is closely related to divergent thinking, which involves the generation of multiple answers to a single problem. Convergent thinking, however, aims to answer a problem with a single, correct solution (Guilford 1967). Participants were assessed using the Alternate Uses Task (AUT) and the Remote Associations Task (RAT). These tasks are used to measure divergent and convergent thinking, respectively. They are also correlated with the spontaneous EBR, a measure of dopamine levels in the striatal pathway. Binaural beats (at 10 or 40 Hz) or the 340 Hz carrier tone alone (control condition) was applied for 3 min before beginning the tasks. The authors reported that both alpha and gamma frequency binaural beats influenced task performance during the divergent, but not convergent thinking task. Participants with a low EBR benefitted from alpha binaural beat stimulation during the divergent thinking task. Those participants with high spontaneous EBRs were either unaffected or impaired by alpha and gamma binaural beat stimulation (Reedijk et al. 2013).

Effect of Binaural Beat Stimulation on Verbal Memory

Research reporting effects of auditory beat stimulation on memory processes is sparse. Currently there are only two such studies, and they report contradictory findings for theta frequency binaural beat stimulation (Wahbeh et al. 2007a; Ortiz et al. 2008) used a subscale of the Wechsler III Memory Scale as a measure of verbal memory. The Wechsler III Memory Scale examines working and long-term memory functions (Wechsler 1945), which in this study was the immediate recall of word lists. The authors observed that binaural beat stimulation at 5 Hz for 15 min, twice a day for 2 weeks, significantly increased the number of words recalled during testing and after stimulation (Ortiz et al. 2008). Wahbeh et al. 2007a, however, reported no significant effect of binaural beat stimulation at 7 Hz, after a single 30 min session. They used the Rey Auditory Verbal Learning Test to measure verbal memory performance. In this case, participants are asked to repeat at list of 15 unrelated words, during different trials. The test examines working and long-term memory performance (Corwin and Rey 1993). Wahbeh et al. (2007a) reported a decrease in immediate verbal memory recall after the binaural beat condition when compared to the control condition (Wahbeh et al. 2007a). These studies tentatively suggest that different binaural beat stimulation protocols may play a role in verbal memory performance.

The Effect of Binaural Beat Stimulation on Anxiety, Mood States and Vigilance

Studies investigating the use of binaural beats to reduce anxiety-related symptoms and to modulate mood states have reported often contradictory and complex findings. Many of these studies employ different stimulation approaches; for example, there are inconsistencies in stimulation durations, or two or more beat stimulation frequencies were combined, at a time. These reasons may somewhat account for some discrepancies between the outcomes reported. In addition, studies reporting significant effects of binaural beat stimulation also note that any apparent effects appear to be short-lived and weak. Differences in methodological approaches, as well as the reporting of mainly subjective rating scores may explain why some studies report contrasting effects.

Impact of Binaural Beats on Anxiety

Some of the first studies to investigate the use of binaural beat stimulation as a potential therapy, targeted anxiety-related symptoms (Le Scouarnec et al. 2001; Padmanabhan et al. 2005). Anxiety can be differentiated in two ways. State anxiety is a temporary increase in anxiety levels due to an event or situation. Trait anxiety is a continually heightened anxious state which is a personal characteristic (Emmelkamp and Ehring 2014). Four studies have examined the possible effects of binaural beat stimulation on anxiety levels. Weiland et al. (2011) treated anxiety patients using sound compositions with either 10 Hz binaural beats embedded within the compositions, or a recording of sounds within a natural setting. The beat simulation was applied for 20 min after which patients filled out the State-Trait Anxiety Inventory (STAI-I) for anxiety level assessment. Weiland et al., reported significant decreases in anxiety scores post stimulation for patients who received binaural beats, compared to the control patient group (Weiland et al. 2011). In a similar study, Padmanabhan et al. treated pre-operative anxiety patients in an emergency room setting. Binaural beats were applied using a commercially available pre-recorded composition at delta frequency. Patient's anxiety scores were also assessed using the STAI-I questionnaire. Padmanabhan et al. (2005) reported a 26.3% decline in anxiety scores, when compared to the placebo audio patient group, which showed an 11.1% reduction in anxiety ratings (Padmanabhan et al. 2005). Similarly, Le Scouarnec et al. (2001) treated patients diagnosed with mild anxiety disorders using recordings of binaural beats in the delta/theta frequency range for 30 min each day, for a total of one month. Patients were also asked to evaluate their anxiety levels using the STAI-I inventory. The authors observed that anxiety scores decreased when patients chose to listen to the recordings of the binaural beat stimuli more often (Le Scouarnec et al. 2001). Wahbeh et al. also reported that patients who received binaural beat stimulation in the delta frequency range showed a significant decrease in trait anxiety scores. In this study, patients listened to binaural beats for 30-60 mins each day, over 60 days (Wahbeh et al. 2007b).

The Effect of Binaural Beats in Modulating Mood States

Lewis et al. (2008) define a mood state as a temporary, conscious state of mind or predominant feeling (Lewis et al. 2008). For the subject or patient, it is often hard to define and dependent upon external factors. The modulation of mood states offers a useful potential therapeutic target for binaural beats. The three studies investigating the effects of beat stimulation on mood states used the Profile of Mood States (POMS) questionnaire to monitor mood changes in patient populations before and after stimulation. The POMS is based on a self-report inventory containing 65 items. Each item is allocated to a mood score and has six subscales. For example, two such subscales are 'Tension-Anxiety' and 'Depression-Dejection' (McNair and Heuchert 2011). In two contrasting studies conducted by Wahbeh et al. (2007a, b), patients were given recordings of binaural beats at either 7 Hz (theta) or 0–4 Hz (delta), and were instructed to listen daily for 60 days, in the case of the delta frequency beats, or once for 30 min in the case of the theta frequency beat stimulation. Patients who received delta frequency beat stimulation reported a decrease in POMS subscales for tension, anxiety, confusion and fatigue, as well as a decrease in total mood disturbance. However, after both delta beat stimulation (daily stimulation sessions over 60 days) and one 30-min theta beat frequency stimulation, patients reported an increase in the POMS depression subscale (Wahbeh et al. 2007a, b). Lane et al. (1998) used a similar approach, and also reported a decrease in POMS depression subscales and associated beat stimulation in the beta range with less negative mood when compared with theta/delta beats. In this study, the authors compared beats in the beta (16 and 24 Hz) frequency range to beats in the theta/delta (1.5 and 4 Hz) frequency range (Lane et al. 1998).

Binaural Beat Frequencies and Vigilance

The ability to maintain a constant focus of attention and alert to stimuli over long periods of time is termed vigilance (Warm et al. 2008). Tasks used to assess vigilance comprise of simple, monotonic sensory processing and require that subjects maintain a level of continuous attention. In an early study investigating the effects of beat stimulation on vigilance and mood, Lane et al. (1998) tested the effects of beta (16 and 24 Hz) and theta/delta (1.5 and 4 Hz) binaural frequencies on a psychomotor vigilance task. Beat stimulation was applied during the task for 30 min. The authors reported that beat stimulation in the beta frequency range was associated with a lower false alarm rate and better correct target detection, compared with beat stimulation in the theta/delta range. Overall beta frequency stimulation for 30 min improved performance of the vigilance task (Lane et al. 1998).

In another study, Goodin et al. (2012) examined the effects of theta (7 Hz) and beta (16 Hz) binaural beats on the interaction between personality traits and vigilance. Based on previous findings by Lane et al. (1998), the authors hypothesized that beat stimulation in the beta range would increase and sustain vigilance levels

during the psychomotor task. Another interesting aspect of the study was the hypothesized interaction between beat stimulation, vigilance and personality traits. In an earlier study, Stough et al. (2001) reported a correlation between personality traits identified using the five-factor model (FFM) (McCrae and John 1992) and cortical entrainment using photic driving. The FFM identifies five main personality traits, Neuroticism (N), Extraversion (E), Openness to experience (O), Agreeableness (A) and Contentiousness (C). Participants exhibiting personality traits O and C were more susceptible to cortical entrainment in the theta and beta bands (Stough et al. 2001). In the study by Goodin et al. (2012), participants were assessed using the FFM, and while they performed the vigilance task were stimulated using theta (7 Hz) and beta (16 Hz) binaural beat frequencies for 4 min. EEG was also recorded throughout the experiment. The authors hypothesized that individuals expressing O and C personality traits would be more susceptible to entrainment in the theta and beta beat frequency ranges, and that individuals who scored higher in trait category A would demonstrate higher beta power in the left temporal and central cortical regions. However, no significant effects of stimulation on the performance of the vigilance task, or interaction with personality traits were observed. The authors concluded that short duration binaural beat stimulation was not sufficient to induce any long-lasting effects (Goodin et al. 2012).

Conclusion

The majority of therapeutic studies reporting effects of auditory beat stimulation have applied binaural beats, and not monaural beats (Padmanabhan et al. 2005; Kennel et al. 2010; Weiland et al. 2011). Studies examining the source of the binaural beat percept, and how it is generated will enable future studies to apply more appropriate stimulation protocols with which to target cognition and mood states. As of now, the cortical networks most involved in processing the effects of binaural beat stimulation have not yet been unambiguously identified.

For studies investigating the effects of binaural beats on mood states and anxiety-related symptoms, we can see that there is often a reduction in negative mood scores and a diminishing effect of anxiety levels reported (Le Scouarnec et al. 2001; Padmanabhan et al. 2005; Weiland et al. 2011). However, differences between beat stimulation approaches make careful comparisons between studies increasingly difficult. This is underlined by the application of more than one beat frequency during a single stimulation session (Lane et al. 1998). However, it seems apparent that the most promising application of binaural beats is to modulate mood states and to possible aid in the treatment of anxiety syndromes, as studies report positive effects.

It is an open question which beat stimulation frequencies are best suited for cognitive enhancement. In a recent study looking at enhancing attentional focus using binaural beats, Colzato et al. (2015) described the relationship between high and low frequency beats and suitable targets. They proposed that low frequency binaural beats

are more likely to be associated with mental relaxation and high-frequency beats with processes relating to attention and alertness (Colzato et al. 2015).

Reedijk et al. (2015) also raise another interesting issue of applying the most suitable binaural beat stimulation parameters based on inter-individual differences. A study examining the effects of beat stimulation applied in the beta and delta ranges also makes this point. Lavallee et al. (2011) showed that differences in entrainment effects between experienced and novice meditation practitioners existed according to their individual experience (Lavallee et al. 2011). Tailoring beat stimulation to individual traits may aid in increasing the efficacy of beat stimulation parameters.

Other factors that may influence the effects of beat stimulation are age and gender. Grose and Mamo (2012) reported that the binaural beat percept in the gamma range was less accurately detected by older individuals (Grose and Mamo 2012). Other studies have reported that gender differences may play a role, not only in binaural beat perception, but also in auditory perception during the menstrual cycle (Oster 1973; Haggard and Gaston 1978).

Further studies aiming to understand the effects of beat stimulation should also take into account the role of monaural beats and whether monaural beat stimulation may be more suitable for some applications. In addition, detailed reporting of stimulation parameters will help to avoid methodological inconsistencies and enable the development of more effective protocols and hypotheses.

References

Barkley, R. A. (2005). *Attention-deficit hyperactivity disorder: A handbook for diagnosis and treatment* (3rd ed.). New York: The Guilford Press.

Becher, A.-K., Höhne, M., Axmacher, N., Chaieb, L., Elger, C. E., & Fell, J. (2014). Intracranial electroencephalography power and phase synchronization changes during monaural and binaural beat stimulation. *The European Journal of Neuroscience, 41*(2), 254–263. doi:10.1111/ejn.12760

Colzato, L. S., Barone, H., Sellaro, R., & Hommel, B. (2015). More attentional focusing through binaural beats: Evidence from the global-local task. *Psychological Research*. doi:10.1007/s00426-015-0727-0

Colzato, L. S., Waszak, F., Nieuwenhuis, S., Posthuma, D. & Hommel, B. (2010). The flexible mind is associated with the catechol-O-methyltransferase (COMT) Val158Met polymorphism: Evidence for a role of dopamine in the control of task-switching. *Neuropsychologia, 48*(9), pp. 2764–2768. doi:10.1016/j.neuropsychologia.2010.04.023

Cools, R. (2008). Role of dopamine in the motivational and cognitive control of behavior. *The Neuroscientist: A Review Journal Bringing Neurobiology, Neurology and Psychiatry, 14*(4), 381–395. doi:10.1177/1073858408317009

Corwin, F. W. B. J., & Rey, A. (1993). Psychological examination of traumatic encephalopathy. *The Clinical Neuropsychologist, 7,* 3–21. doi:10.1080/13854049308401883

Draganova, R., Ross, B., Borgmann, C., & Pantev, C. (2002). Auditory cortical response patterns to multiple rhythms of AM sound. *Ear and Hearing, 23*(3), 254–265.

Draganova, R., Ross, B., Wollbrink, A., & Pantev, C. (2008). Cortical steady-state responses to central and peripheral auditory beats. *Cerebral Cortex, 18*(5), 1193–1200. doi:10.1093/cercor/bhm153

Dreisbach, G., Müller, J., Goschke, T., Strobel, A., Schulze, K., Lesch, K.-P. and Brocke, B. (2005). Dopamine and cognitive control: The influence of spontaneous eyeblink rate and dopamine gene polymorphisms on perseveration and distractibility. *Behavioral Neuroscience, 119*(2), 483–490. doi:10.1037/0735-7044.119.2.483

Emmelkamp, P., & Ehring, T. (2014). *The Wiley handbook of anxiety disorders*. Accessed April 14, 2015, from http://eu.wiley.com/WileyCDA/WileyTitle/productCd-111877535X.html

Fell, J., & Axmacher, N. (2011). The role of phase synchronization in memory processes. *Nature Reviews Neuroscience, 12*(2), 105–118. doi:10.1038/nrn2979

Galambos, R., Makeig, S., & Talmachoff, P. J. (1981). A 40-Hz auditory potential recorded from the human scalp. *Proceedings of the National Academy of Sciences of the United States of America, 78*(4), 2643–2647.

Gao, X., Cao, H., Ming, D., Qi, H., Wang, X., Wang, X., et al. (2014). Analysis of EEG activity in response to binaural beats with different frequencies. *International Journal of Psychophysiology: Official Journal of the International Organization of Psychophysiology, 94*(3), 399–406. doi:10.1016/j.ijpsycho.2014.10.010

Goodin, P., Ciorciari, J., Baker, K., Carey, A.-M., Carrey, A.-M., Harper, M., et al. (2012). A high-density EEG investigation into steady state binaural beat stimulation. *PLoS ONE, 7*(4), e34789. doi:10.1371/journal.pone.0034789

Grose, J. H., & Mamo, S. K. (2012). Electrophysiological measurement of binaural beats: Effects of primary tone frequency and observer age. *Ear and Hearing, 33*(2), 187–194. doi:10.1097/AUD.0b013e318230bbbd

Guilford, J. P. (1967). *The nature of human intelligence*. New York: McGraw-Hill.

Haggard, M., & Gaston, J. B. (1978). Changes in auditory perception in the menstrual cycle. *British Journal of Audiology, 12*(4), 105–118.

Karino, S., Yumoto, M., Itoh, K., Uno, A., Yamakawa, K., Sekimoto, S., et al. (2006). Neuromagnetic responses to binaural beat in human cerebral cortex. *Journal of Neurophysiology, 96*(4), 1927–1938. doi:10.1152/jn.00859.2005

Kennel, S., Taylor, A. G., Lyon, D., & Bourguignon, C. (2010). Pilot feasibility study of binaural auditory beats for reducing symptoms of inattention in children and adolescents with attention-deficit/hyperactivity disorder. *Journal of Pediatric Nursing, 25*(1), 3–11. doi:10.1016/j.pedn.2008.06.010

Kuwada, S., Yin, T. C., & Wickesberg, R. E. (1979). Response of cat inferior colliculus neurons to binaural beat stimuli: Possible mechanisms for sound localization. *Science, 206*(4418), 586–588.

Lane, J. D., Kasian, S. J., Owens, J. E., & Marsh, G. R. (1998). Binaural auditory beats affect vigilance performance and mood. *Physiology & Behavior, 63*(2), 249–252.

Lavallee, C. F., Koren, S. A., & Persinger, M. A. (2011). A quantitative electroencephalographic study of meditation and binaural beat entrainment. *Journal of Alternative and Complementary Medicine, 17*(4), 351–355. doi:10.1089/acm.2009.0691

Lewis, M., Haviland-Jones, J. M., & Barrett, L. F. (2008). *Handbook of emotions* (3rd ed.). New York: Guilford.

Licklider, J. C. R., Webster, J. C., & Hedlun, J. M. (1950). On the frequency limits of binaural beats. *The Journal of the Acoustical Society of America, 22*(4), 468–473. doi:10.1121/1.1906629

McCrae, R. R., & John, O. P. (1992). An introduction to the five-factor model and its applications. *Journal of Personality, 60*(2), 175–215. doi:10.1111/j.1467-6494.1992.tb00970.x

McNair, D. M., & Heuchert, J. P. (2011). *Profile of mood states* (2nd ed.). JvR Psychometrics Assessment Catalogue. Accessed April 14, 2015, from http://catalogue.jvrpsychometrics.co.za/profile-of-mood-states/

Ortiz, T., Martínez, A. M., Fernández, A., Maestu, F., Campo, P., Hornero, R., et al. (2008). Impact of auditory stimulation at a frequency of 5 Hz in verbal memory. *Actas Españolas De Psiquiatría, 36*(6), 307–313.

Oster, G. (1973). Auditory beats in the brain. *Scientific American, 229*(4), 94–102.

Padmanabhan, R., Hildreth, A. J., & Laws, D. (2005). A prospective, randomised, controlled study examining binaural beat audio and pre-operative anxiety in patients undergoing general anaesthesia for day case surgery. *Anaesthesia, 60*(9), 874–877. doi:10.1111/j.1365-2044.2005.04287.x

Pantev, C., Roberts, L. E., Elbert, T., Ross, B., & Wienbruch, C. (1996). Tonotopic organization of the sources of human auditory steady-state responses. *Hearing Research, 101*(1–2), 62–74.

Picton, T. W., John, M. S., Dimitrijevic, A., & Purcell, D. (2003). Human auditory steady-state responses. *International Journal of Audiology, 42*(4), 177–219.

Pratt, H., Starr, A., Michalewski, H. J., Dimitrijevic, A., Bleich, N., & Mittelman, N. (2009). Cortical evoked potentials to an auditory illusion: Binaural beats. *Clinical Neurophysiology: Official Journal of the International Federation of Clinical Neurophysiology, 120*(8), 1514–1524. doi:10.1016/j.clinph.2009.06.014

Pratt, H., Starr, A., Michalewski, H. J., Dimitrijevic, A., Bleich, N., & Mittelman, N. (2010). A comparison of auditory evoked potentials to acoustic beats and to binaural beats. *Hearing Research, 262*(1–2), 34–44. doi:10.1016/j.heares.2010.01.013

Raymond, J. E., Shapiro, K. L., & Arnell, K. M. (1992). Temporary suppression of visual processing in an RSVP task: an attentional blink? *Journal of Experimental Psychology: Human Perception and Performance, 18*(3), 849–860.

Reedijk, S. A., Bolders, A., Colzato, L. S., & Hommel, B. (2015). Eliminating the attentional blink through binaural beats: A case for tailored cognitive enhancement. *Frontiers in Psychiatry, 6,* 82. doi:10.3389/fpsyt.2015.00082

Reedijk, S. A., Bolders, A., & Hommel, B. (2013). The impact of binaural beats on creativity. *Frontiers in Human Neuroscience, 7,* 786. doi:10.3389/fnhum.2013.00786

Ross, B., Draganova, R., Picton, T. W., & Pantev, C. (2003). Frequency specificity of 40-Hz auditory steady-state responses. *Hearing Research, 186*(1–2), 57–68.

Ross, B., Miyazaki, T., Thompson, J., Jamali, S., & Fujioka, T. (2014). Human cortical responses to slow and fast binaural beats reveal multiple mechanisms of binaural hearing. *Journal of Neurophysiology*. doi:10.1152/jn.00224.2014

Schnupp, J., Nelken, I., & King, A. (2012). *Auditory neuroscience: Making sense of sound*. Cambridge, MA: MIT.

Schwarz, D. W. F., & Taylor, P. (2005). Human auditory steady state responses to binaural and monaural beats. *Clinical Neurophysiology: Official Journal of the International Federation of Clinical Neurophysiology, 116*(3), 658–668. doi:10.1016/j.clinph.2004.09.014

Scouarnec, Le., Poirier, R. M., Owens, J. E., Gauthier, J., Taylor, A. G., & Foresman, P. A. (2001). Use of binaural beat tapes for treatment of anxiety: A pilot study of tape preference and outcomes. *Alternative Therapies in Health and Medicine, 7*(1), 58–63.

Squire, L. R., Bloom, F. E., & Spitzer, N. C. (2008). *Fundamental neuroscience* (4th ed.). Amsterdam: Academic Press.

Stough, C., Donaldson, C., Scarlata, B., & Ciorciari, J. (2001). Psychophysiological correlates of the NEO PI-R openness, agreeableness and conscientiousness: Preliminary results. *International Journal of Psychophysiology: Official Journal of the International Organization of Psychophysiology, 41*(1), 87–91.

Vernon, D., Peryer, G., Louch, J., & Shaw, M. (2012). Tracking EEG changes in response to alpha and beta binaural beats. *International Journal of Psychophysiology: Official Journal of the International Organization of Psychophysiology*. doi:10.1016/j.ijpsycho.2012.10.008

Wahbeh, H., Calabrese, C., Zwickey, H., & Zajdel, D. (2007a). Binaural beat technology in humans: A pilot study to assess neuropsychologic, physiologic, and electroencephalographic effects. *Journal of Alternative and Complementary Medicine, 13*(2), 199–206. (New York, NY). doi:10.1089/acm.2006.6201

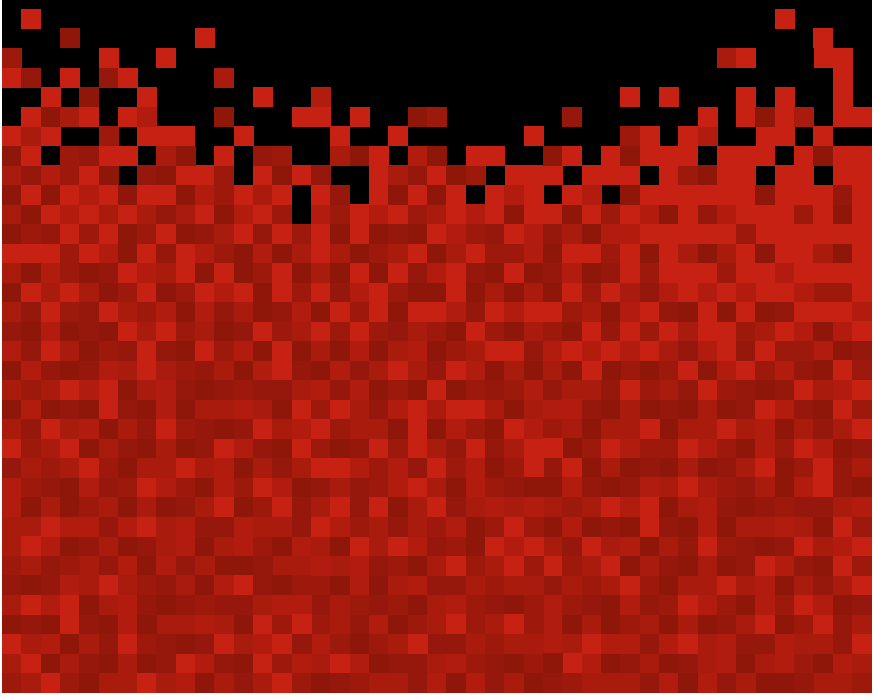
Wahbeh, H., Calabrese, C., & Zwickey, H. (2007b). Binaural beat technology in humans: A pilot study to assess psychologic and physiologic effects. *Journal of Alternative and Complementary Medicine, 13*(1), 25–32. doi:10.1089/acm.2006.6196

Warm, J. S., Parasuraman, R., & Matthews, G. (2008). Vigilance requires hard mental work and is stressful. *Human Factors: The Journal of the Human Factors and Ergonomics Society, 50*(3), 433–441. doi:10.1518/001872008X312152

Wechsler, D. (1945). *Wechsler memory scale*. San Antonio, TX: Psychological Corporation.

Weiland, T. J., Jelinek, G. A., Macarow, K. E., Samartzis, P., Brown, D. M., Grierson, E. M., et al. (2011). Original sound compositions reduce anxiety in emergency department patients: A randomised controlled trial. *The Medical Journal of Australia, 195*(11–12), 694–698.

far transfer trainings:
generalizing
learned
skills



Part V
Far Transfer Trainings—Generalizing Learned Skills

Introduction

The interest in our daily-life-influencing practices such as musical experience, video games, sports, and meditation is constantly growing. In the past decade, this has inspired several investigations on the potential cognitive benefits that having learned to play musical instruments, playing video games, engaging in physical activity and undertaking meditation sessions may have on players/practitioners. It is well known that musicians (see Chapter "Musical Training"), gamers (see Chapter "Video Games"), athletes (see Chapter "Aerobic Exercise"), and meditators (see Chapter "Meditation") have been reported to be better than naive people in skills related to their practice of preference, which however mainly indicate the effectiveness of the training programs. However, in the present part, we will discuss increasing evidence that musical, video game, aerobic and meditation training promote both untrained, but related skills, and entirely unrelated skills—which amounts to near and far transfer in cognitive-training terms (Li et al. 2008).

Accordingly, in the following chapters, the available behavioral and neuroscientific studies of these far transfer effects will be reviewed in order to elucidate the degree to which these trainings generalize to, and enhance cognitive functions not directly or unrelated to them.

Reference

Li, S.-C., Schmiedek, F., Huxhold, O., Röcke, C., Smith, J., & Lindenberger, U. (2008). Working memory plasticity in old age: Practice gain, transfer, and maintenance. *Psychology and Aging, 23*, 731–742.

RETRACTED CHAPTER: Musical Training

Lorenza S. Colzato

Introduction

The interest in the influence of musical experience on our daily life is constantly growing. Similar to meditation, in the field of healthcare and stress management, music has been shown to enhance positive feelings, increase pain tolerance, and reduce anxiety (Voss et al. 2004). Encompassing the clinical settings, in the past decade, various studies have focused instead on the possible cognitive benefits that having learned to play musical instruments may have on the players. Not surprisingly, musicians have been reported to be better than non-musicians in various music-related skills (see Schellenberg 2005; Zatorre et al. 2007, for reviews on the topic), which however mainly demonstrate the efficiency of the training program. Interestingly, however, similarly to other fields such as video gaming (see Chapter "Video games"), aerobic exercise (see Chapter "Aerobic exercise") and meditation (see Chapter "Meditation"), there is increasing evidence that musical training enhances both untrained but related skills and entirely unrelated skills—which amounts to near and far transfer in cognitive training terms (Li et al. 2008), respectively.

In this chapter, adapted from Benz et al. (2015), I will first describe the effect of musical training on neuroplasticity as a possible underlying mechanism of action. Second, I will outline the available behavioral and neuroscientific studies on these kinds of effects and assess the degree to which musical exercise generalizes to cognitive functions not directly or unrelated to musical abilities in healthy humans.

The original version of this chapter was retracted: The retraction note to this chapter is available at https://doi.org/10.1007/978-3-319-57505-6_24

L.S. Colzato (✉)
Cognitive Psychology Unit and Leiden Institute for Brain and Cognition, Leiden University, Leiden, The Netherlands
e-mail: colzato@fsw.leidenuniv.nl

L.S. Colzato
Institute of Cognitive Neuroscience, Faculty of Psychology, Ruhr University Bochum, Bochum, Germany

L.S. Colzato, *Theory-Driven Approaches to Cognitive Enhancement*,
https://doi.org/10.1007/978-3-319-57505-6_13

The studies indicate that musical training is associated with enhancing effects, even if sometimes only restricted to the auditory domain, on various cognitive functions spanning from executive control to creativity.

Mechanism of Action: Neuroplasticity

Jäncke (2009) suggested that learning to play an instrument induces structural and functional changes in the brain, due to the continuous activation of the brain regions underlying or engaged by these learning processes. Of particular interest for our purposes, differences between musician and non-musicians might be visible not only in brain areas related to the processing of visual and auditory information but also in frontal regions related to higher order cognitive control processes involved in producing music. Using voxel-based morphometry, researchers have analyzed gray matter density of people that varied with respect to the intensity of musical training (James et al. 2014). Greater musical expertise was associated with increased gray matter density in the left inferior frontal gyrus, which is involved in syntactic processing, executive functions, and working memory, and in the left intraparietal sulcus responsible for visuomotor coordination. Gray matter density was also significantly increased in brain areas involved in visual pattern recognition (right fusiform gyrus) and in tonal sensitivity (right mid orbital gyrus).

Previous studies have reported musician-enhanced neuroplasticity effects not just during childhood (e.g., Hyde et al. 2009a, b), which is typically much more sensitive to plastic changes, but also across the life span. For instance, a very recent school-based longitudinal study has provided evidence that in-school musical training can affect developmental plasticity even when it is begun in adolescence (Tierney et al. 2015)—a finding that suggests that adolescent brain is still receptive to training notwithstanding the fact that childhood-associated plasticity has started to decline (Penhune 2011). Along the same lines, a new study by Vaquero et al. (2016) has shown that structural neuroplasticity in expert pianists depends also on the age of musical training onset. Further, another very recent study has shown that such an association between musical training and neuroplastic benefits extends to older individuals for whom plasticity is even weaker (Bidelman and Alain 2015). Specifically, it was found that, compared to older adults with little-to-no musical training experience, older musicians showed increased neuroplasticity in auditory stem and cortex. This finding is particularly intriguing as it suggests that musical training can have long-lasting effects to the extent that life-long musical engagement can potentially compensate for neuroplastic age-related declines in auditory brain processing associated with normal aging. This implies that life-long musical training may provide musicians with a cognitive reserve that could delay or even reverse age-related cognitive declines (Alain et al. 2014). However, more research is needed to verify musical training impact on the aged brain and to provide evidence for a causal relationship between musical experience and neuroplasticity in the elderly.

In sum, it seems that enhancing effect associated with musical training may be due to neuroplasticity: structural and functional changes in the brain caused by the learning processes of playing an instruments.

Music Promotes Phonemic Awareness, Reading and Language Abilities

As pointed out in the introduction, it is not surprising that engaging in learning a music instrument is related to an enhancement of music-related abilities. For instance, 2 years in-school music training was found to improve the neurophysiological discrimination of similar speech sounds in children at high risk for learning problems (Kraus et al. 2014). Similar studies have shown that children who underwent years of musical training excelled in the discrimination of small pitch variations in melodies (Magne et al. 2006; Moreno et al. 2009). Neurophysiological studies of the same sort have shown that this skill is accompanied by an increase of error-related negativity in the event-related-potential Event-Related-Potential (ERP) when listening to incongruent tones as well as shorter latencies in positive ERP components (Magne et al. 2006; Moreno et al. 2009). Interestingly, this enhancement in the discrimination of pitch variation in melodies was associated with better performance in the discrimination of small pitch variations in spoken sentences as well—an indication of at least medium transfer of musical training. It is possible that this observation is related to the finding that people suffering from dyslexia have more deficits in a pitch discrimination task when they have to find variations in frequency in normal tones than controls (Baldeweg et al. 1999; Santos et al. 2007). Moreover, in preschoolers there seems to be a link between phonological awareness, the ability to conceive the tone structure of a heard words, musical skills, and reading abilities (Anvari et al. 2002): more musical abilities were positively correlated with better reading abilities and phonemic awareness. All these findings suggest that phonological awareness and music perception may share the same underlying structural mechanisms. Additional evidence supporting the possibility that musical training may have a positive effect on linguistic abilities comes from two recent longitudinal studies in which 8- to 10-year-old children underwent a 2-year music or painting training program (François et al. 2013; Chobert et al. 2014). Compared to children who were assigned to the painting training, those assigned to the music training showed improved speech segmentation skills (François et al. 2013) and enhanced preattentive processing of syllabic duration and voice onset time already after 12 months of training (Chobert et al. 2014). Along the same lines, Slater et al. (2015) reported the first longitudinal evidence that speech-in-noise perception improves after 2 years of group music training.

The influential shared syntactic integration resource hypothesis by Patel (2003) has postulated shared processing structure in language and music, which may account for the observed transfer effects (for an extensive discussion, see Moreno and Bidelman 2013; White et al. 2013). Evidence favoring this possibility was

recently provided by the study of Moreno et al. (2015), in which 4- to 6-year-old children underwent to a 4-week of either a language or a music training. At the post-training evaluation, both groups showed improved processing of trained sounds, which was associated with a better ability to suppress irrelevant (untrained) sounds. Importantly, identical (although attenuated) training-related effects were observed at a follow-up evaluation carried out 1-year after the training intervention.

Very recently Slevc and Okada (2015) have suggested that one shared resource of language and music may be the prefrontal cortex, which is known to be involved in the detection and resolution of conflicts and violations of expectations (van Veen and Carter 2006). As musical processing encompasses the online processing and integration of musical elements together with the generation of musical predictions and expectations, musical training may well strengthen the ability to detect and deal with conflict.

All in all, musical training seems to promote phonemic awareness, reading, and language abilities.

Enhancing Effect on Executive Function, Verbal Memory, and Visual Attention

Making music with an instrument requires several skills involving executive functions: notes have to be played in the correct sequence, with the correct duration and the right temporal distance between them. Indeed, musicians outperformed non-musicians in conflict monitoring tasks suggesting that extended musical experience enhances executive control (Bialystok and DePape 2009). Even though a recent study has found no evidence of enhanced visual memory ability in musicians compared to non-musicians (Rodrigues et al. 2014), long-term musical training has been found to be related to improvements in working memory (George and Coch 2011) in both auditory and visual domains and in terms of both behavioral (faster WM updating) and ERP measures (larger amplitude P300). Along the same lines, musicians outperformed non-musicians in working memory for musical sounds due to an enhanced ability to exert sustained cognitive control (Pallesen et al. 2010). Consistent with this picture, adult musicians compared to non-musicians showed enhanced performance on measures of cognitive flexibility and working memory (Zuk et al. 2014), again supporting the hypothesis that musical training facilitates the development and maintenance of certain executive functions. Along the same lines, Moradzadeh et al. (2015) found that musicians, compared with non-musicians, showed enhanced ability to shift flexibly between mental sets and in dual task performance. Moreover, in a seminal longitudinal study by Bergman Nutley et al. (2014) participants' performance was evaluated at two/three time points, two years apart. It was found that musical practice was positively associated with both visuospatial and verbal WM capacity across all three time points. Interestingly, fluctuations in WM between the time points were proportional to the weekly hours spent on musical practice. Further, in older adults a piano training

intervention of 4 months, compared to an active control intervention, was enough to find a significant improvement in inhibitory control (Seinfeld et al. 2013) suggesting that playing piano and learning to read music can be a useful intervention in older adults in order to compensate for cognitive decline.

Several studies investigated whether musical training improves verbal memory. In comparison to non-musicians, musicians remembered more words from a recently presented word-list (Chan et al. 1998). This finding is consistent with a study in which musicians showed superior performance in verbal memory and reasoning in comparison to non-musicians (Brandler and Rammsayer 2003). Verbal memory span seems also enhanced with musical training supporting the idea of superior verbal rehearsal mechanisms in musicians (Franklin et al. 2008).

Visual attention also seems to be improved in musicians (Rodrigues et al. 2013). This finding was confirmed by a recent longitudinal study in which musical training was found to increase visual attention over time (Roden et al. 2014). Very recently, Martens et al. (2015) investigated musical training on the allocation of attention over time as indexed by the "attentional blink (AB)"—when two target stimuli (T1 and T2) embedded in a rapid stream of events are presented in close temporal proximity, the second target stimulus is often not noticed. People who were musically trained showed an attenuated and delayed AB when required to identify two auditory targets amongst a stream of non-targets, probably reflecting a more efficient allocation of attention. However, this effect was restricted to the auditory domain and did not transfer to the visual domain suggesting a domain-specific effect.

All in all, musical training seems to promote executive functions, verbal memory, and visual attention even though in some cases the enhancing effect is only restricted to the auditory domain.

More Creative, Faster, and Intelligent Because of Music?

Information processing speed is an important mental ability for learning. Musical training seems to have a beneficial effect on processing speed: adolescents with years of active musical experience showed better performance in both visual and auditory information processing speed tasks than non-musicians (Bugos and Mostafa 2011). These findings may suggest that musical training influences the integration of visual and acoustic information with complex motor patterns. Consistent with this picture, a longitudinal study has shown better performance in processing speed tasks in a group of children who followed musical training for one year compared to children who followed a science training (Roden et al. 2014). Additional evidence comes from the already earlier mentioned study by Bergman Nutley et al. (2014), in which music training, besides improving WM, was also found to improve processing speed and reasoning ability (i.e., fluid intelligence). These findings are particularly intriguing given the relation between WM and processing speed (Fry and Hale 2000), and the strong connection of this

relationship with the construct of intelligence. The possibility that reasoning ability may benefit from music training is indeed supported by other findings. After 30 weeks, children receiving music instruction improved in the Binet intelligence subscale involving spatial-temporal reasoning abilities (Bilhartz et al. 1999). Along the same lines, Schellenberg (2004) found that music lessons, compared to drama lessons or no lessons, enhance IQ, as measured by WISC-III (Wechsler 1991). Schellenberg (2006) reported a long-lasting association between formal exposure to music in childhood and both IQ and academic performance. Moreover, Moreno et al. (2011) pointed out that even a shorter term music training of 20 days was enough to enhance verbal intelligence in children. Finally, Schellenberg (2011) suggested that the link between musical training and IQ may not be mediated by executive functions but children with higher IQs may be more likely than children with lower IQs to take music lessons.

Finally, a near-infrared spectroscopy study has shown musical experience to be associated with greater bilateral frontal activity in musicians compared with non-musicians, during divergent thinking (Gibson et al. 2009). However, more recently, Woodward and Sikes (2015) challenged the notion that musical training enhances creativity in general. They found that musicians scored significantly higher on general creativity assessments than non-musicians only when the tests involved the use of sound stimuli to elicit original responses. In contrast, no significant differences between the two groups when the general creativity assessments involved the use of words and imagery. Further, Sovansky et al. (2016) investigated how level of music expertise and engagement in the creation of music relate to divergent thinking. Outcomes revealed that musicians who create music listed more creative uses for music items than non-musicians and musicians who do not create music. However, for non-music items, participants did not display differences in divergent thinking.

In sum, musical training seems to promote intelligence and creativity even though in the case of creativity, the enhancing effect is only restricted to the musical related items.

Conclusion

All in all, the studies reviewed in this chapter points to an association of musical training and enhanced cognitive performance spanning from executive functions to creativity. That is, even if in some cases the benefits were restricted to the auditory domain, the available studies suggest that musical experience is linked to benefits in unpracticed tasks and cognitive functions unrelated (or at least not obviously related) to musical abilities. However, it is important to note that the causal relation between the observed benefits and musical experience may not be straightforward, although the results of the reviewed longitudinal studies are encouraging. Furthermore, as pointed out by Schubert and Strobach (2012), in training studies in general, expectation effects may contribute to a possible confound in interpreting

the results because the knowledge of a study's hypothesis may change subjects' behavior in the study. Second, it would be advisable to employ large test batteries which enable the interpretation of the results in terms of level of cognitive processes and not individual tasks (Green et al. 2014). Additionally, the selection of the proper control group is a relevant issue in musical training. Indeed, active control groups are required given that simple test–retest or passive control group do not rule out potential confounds that do not permit a meaningful interpretation of the results. As pointed out by Schellenberg (2005), ideally, the active control should be another activity from the arts, such as drama training. The good thing of such an active control is that it is typically adaptive by nature (i.e., theater lessons tend to increase in difficulty according to the progression of the acting course). Moreover, it is necessary to exclude that personality (Corrigall et al. 2013) and preexisting neuro-developmental factors may play a mediating role. For instance, individuals with a genetic predisposition that favors executive control functions might be drawn to music more strongly, so that what looks like an effect of practice might actually represent a kind of self-selection. Addressing this issue will require (more) longitudinal studies (Roden et al. 2014; Bergman Nutley et al. 2014). Finally, similarly to other fields of cognitive training (Colzato et al. 2014), it may be interesting to consider individual differences more systematically. Indeed, if musical training really affects neuroplasticity, it makes sense to assume that the effect of music on performance depends on the preexperimental performance level of the individual—be it in terms of compensation (so that worse performers benefit more) or predisposition (so that some are more sensitive to music interventions).

In sum, this chapter sheds light on the potential association of musical training for optimizing cognition in general. Similarly to video game practice (see Chapter "Video games"), aerobic exercise (see Chapter "Aerobic exercise") and meditation (see Chapter "Meditation"), musical engagement may be a useful cognitive training to promote cognitive enhancement in inexpensive, efficient, and healthy ways—perhaps even for those not genuinely interested in music. In particular, musical training may be a very valuable approach to counteract the deteriorative effect of aging on cognitive functioning (Bidelman and Alain 2015).

References

Alain, C., Zendel, B. R., Hutka, S., & Bidelman, G. M. (2014). Turning down the noise: The benefit of musical training on the aging auditory brain. *Hearing Research, 308,* 162–173.

Anvari, S. H., Trainor, L. J., Woodside, J., & Levy, B. A. (2002). Relations among musical skills, phonological processing and early reading ability in preschool children. *Journal of Experimental Child Psychology, 83*(2), 111–130.

Baldeweg, T., Richardson, A., Watkins, S., Foale, C., & Gruzelier, J. (1999). Impaired auditory frequency discrimination in dyslexia detected with mismatch evoked potentials. *Annals of Neurology, 45,* 495–503.

Benz, S., Sellaro, R., Hommel, B., & Colzato, L. S. (2015). Music makes the world go round: The impact of musical training on non-musical cognitive functions—A review. *Frontiers in Psychology, 6,* 2023.

Bergman Nutley, S., Darkiand, F., & Klingberg, T. (2014). Music practice is associated with development of working memory during childhood and adolescence. *Frontiers in Human Neuroscience, 7,* 1–9.

Bialystok, E., & DePape, A. M. (2009). Musical expertise, bilingualism, and executive functioning. *Journal of Experimental Psychology: Human Perception and Performance, 35*(2), 565.

Bidelman, G. M., & Alain, C. (2015). Musical training orchestrates coordinated neuroplasticity in auditory brainstem and cortex to counteract age-related declines in categorical vowel perception. *Journal of Neuroscience, 35*(3), 1240–1249.

Bilhartz, T. D., Bruhn, R. A., & Olson, J. E. (1999). The effect of early music training on child cognitive development. *Journal of Applied Developmental Psychology, 20*(4), 615–636.

Brandler, S., & Rammsayer, T. H. (2003). Differences in mental abilities between musicians and non-musicians. *Psychology of Music, 31*(2), 123–138.

Bugos, J., & Mostafa, W. (2011). Musical training enhances information processing speed. *Bulletin of the Council for Research in Music Education, 187,* 7–18.

Chan, A. S., Ho, Y. C., & Cheung, M. C. (1998). Music training improves verbal memory. *Nature, 396,* 128.

Chobert, J., François, C., Velay, J. L., & Besson, M. (2014). Twelve months of active musical training in 8-to 10-year-old children enhances the preattentive processing of syllabic duration and voice onset time. *Cerebral Cortex, 24*(4), 956–967.

Colzato, L. S., van den Wildenberg, W., & Hommel, B. (2014). Cognitive control and the COMT Val158Met polymorphism: Genetic modulation of videogame training and transfer to task-switching efficiency. *Psychological Research, 78,* 670–678.

Corrigall, K. A., Schellenberg, E. G., & Misura, N. M. (2013). Music training, cognition, and personality. *Frontiers in Psychology, 4,* 222.

François, C., Chobert, J., Besson, M., & Schön, D. (2013). Music training for the development of speech segmentation. *Cerebral Cortex, 23*(9), 2038–2043.

Franklin, M. S., Moore, K. S., Yip, C.-Y., Jonides, J., Rattray, K., & Moher, J. (2008). The effects of musical training on verbal memory. *Psychology of Music, 36*(3), 252–265.

Fry, A. F., & Hale, S. (2000). Relationships among processing speed, working memory, and fluid intelligence in children. *Biological Psychology, 54,* 1–34.

George, E. M., & Coch, D. (2011). Music training and working memory: An ERP study. *Neuropsychologia, 49*(5), 1083–1094.

Gibson, C., Folley, B. S., & Park, S. (2009). Enhanced divergent thinking and creativity in musicians: A behavioral and near-infrared spectroscopy study. *Brain and Cognition, 69*(1), 162–169.

Green, C. S., Strobach, T., & Schubert, T. (2014). On methodological standards in training and transfer experiments. *Psychological Research, 78*(6), 756–772.

Hyde, K. L., Lerch, J., Norton, A., Forgeard, M., Winner, E., Evans, A. C., et al. (2009a). Musical training shapes structural brain development. *The Journal of Neuroscience, 29*(10), 3019–3025.

Hyde, K. L., Lerch, J., Norton, A., Forgeard, M., Winner, E., Evans, A. C., et al. (2009b). The effects of musical training on structural brain development. *Annals of the New York Academy of Sciences, 1169*(1), 182–186.

James, C. E., Oechslin, M. S., Van De Ville, D., Hauert, C. A., Descloux, C., & Lazeyras, F. (2014). Musical Training intensity yields opposite effects on grey matter density in cognitive versus sensorimotor networks. *Brain Structure & Function, 219*(1), 353–366.

Jäncke, L. (2009). The plastic human brain. *Restorative Neurology and Neuroscience, 27,* 521–538.

Kraus, N., Slater, J., Thompson, E. C., Hornickel, J., Strait, D. L., Nicol, T., et al. (2014). Music enrichment programs improve the neural encoding of speech in at-risk children. *The Journal of Neuroscience, 34*(36), 11913–11918.

Li, S.-C., Schmiedek, F., Huxhold, O., Röcke, C., Smith, J., & Lindenberger, U. (2008). Working memory plasticity in old age: Practice gain, transfer, and maintenance. *Psychology and Aging, 23,* 731–742.

Magne, C., Schön, D., & Besson, M. (2006). Musician children detect pitch violations in both music and language better than nonmusician children: Behavioral and electrophysiological approaches. *Journal of Cognitive Neuroscience, 18*(2), 199–211.

Martens, S., Wierda, S. M., Dun, M., de Vries, M., & Smid, H. G. O. M. (2015). Musical minds: Attentional blink reveals modality-specific restrictions. *PLoS One, 10*(2), e0118294.

Moradzadeh, L., Blumenthal, G., & Wiseheart, M. (2015). Musical training, bilingualism, and executive function: A closer look at task switching and dual-task performance. *Cognitive Science, 39*(5), 992–1020.

Moreno, S., Bialystok, E., Barac, R., Schellenberg, E. G., Cepeda, N. J., & Chau, T. (2011). Short-term music training enhances verbal intelligence and executive function. *Psychological Science, 22*(11), 1425–1433.

Moreno, S., & Bidelman, G. M. (2013). Examining neural plasticity and cognitive benefit through the unique lens of musical training. *Hearing Research, 308,* 84–97. doi:10.1016/j.heares.2013.09.012

Moreno, S., Marques, C., Santos, A., Santos, M., Castro, S. L., & Besson, M. (2009). Musical training influences linguistic abilities in 8-year-old children: More evidence for brain plasticity. *Cerebral Cortex, 19,* 712–723.

Moreno, S., Lee, Y., Janus, M., & Bialystok, E. (2015). Short-term second language and music training induces lasting functional brain changes in early childhood. *Child Development, 86*(2), 394–406.

Pallesen, K. J., Brattico, E., Bailey, C. J., Korvenoja, A., Koivisto, J., & Gjedde, A. (2010). Cognitive control in auditory working memory is enhanced in musicians. *PLoS One, 5*(6), e11120.

Patel, A. D. (2003). Language, music, syntax and the brain. *Nature Neuroscience, 6*(7), 674–681.

Penhune, V. B. (2011). Sensitive periods in human development: Evidence from musical training. *Cortex, 47*(9), 1126–1137.

Roden, I., Könen, T., Bongard, S., Frankenberg, E., Friedrich, E. K., & Kreutz, G. (2014). Effects of music training on attention, processing speed and cognitive music abilities—Findings from a longitudinal study. *Applied Cognitive Psychology, 28*(4), 545–557.

Rodrigues, A. C., Loureiro, M. A., & Caramelli, P. (2013). Long-term musical training may improve different forms of visual attention ability. *Brain and Cognition, 82*(3), 229–235.

Rodrigues, A. C., Loureiro, M., & Caramelli, P. (2014). Visual memory in musicians and non-musicians. *Frontiers in Human Neuroscience, 8,* 424.

Santos, A., Joly-Pottuz, B., Moreno, S., Habib, M., & Besson, M. (2007). Behavioural and event-related potentials evidence for pitch discrimination deficits in dyslexic children: Improvement after intensive phonic intervention. *Neuropsychologia, 45,* 1080–1109.

Schellenberg, E. G. (2004). Music lessons enhance IQ. *Psychological Science, 15*(8), 511–514.

Schellenberg, E. G. (2005). Music and cognitive abilities. *Current Directions in Psychological Science, 14*(6), 317–320.

Schellenberg, E. G. (2006). Long-term positive associations between music lessons and IQ. *Journal of Educational Psychology, 98*(2), 457.

Schellenberg, E. G. (2011). Examining the association between music lessons and intelligence. *British Journal of Psychology, 102*(3), 283–302.

Schubert, T., & Strobach, T. (2012). Video game experience and optimized executive control skills—On false positives and false negatives: Reply to Boot and Simons. *Acta Psychologica, 141*(2), 278–280.

Seinfeld, S., Figueroa, H., Ortiz-Gil, J., & Sanchez-Vives, M. V. (2013). Effects of music learning and piano practice on cognitive function, mood and quality of life in older adults. *Frontiers in Psychology, 4,* 103389.

Slater, J., Skoe, E., Strait, D. L., O'Connell, S., Thompson, E., & Kraus, N. (2015). Music training improves speech-in-noise perception: Longitudinal evidence from a community-based music program. *Behavioural brain research, 291,* 244–252.

Slevc, L. R., & Okada, B. M. (2015). Processing structure in language and music: A case for shared reliance on cognitive control. *Psychonomic Bulletin & Review, 22*(3), 637–652.

Sovansky, E. E., Wieth, M. B., Francis, A. P., & McIlhagga, S. D. (2016). Not all musicians are creative: Creativity requires more than simply playing music. *Psychology of Music, 44,* 25–36.

Tierney, A. T., Krizman, J., & Kraus, N. (2015). Music training alters the course of adolescent auditory development. *Proceedings of the National Academy of Sciences, 112*(32), 10062–10067.

van Veen, V., & Carter, C. S. (2006). Conflict and cognitive control in the brain. *Current Directions in Psychological Science, 15*(5), 237–240.

Vaquero, L., Hartmann, K., Ripollés, P., Rojo, N., Sierpowska, J., François, C., … Münte, T. F. (2016). Structural neuroplasticity in expert pianists depends on the age of musical training onset. *NeuroImage, 126*, 106–119

Voss, J. A., Good, M., Yates, B., Baun, M. M., Thompson, A., & Hertzog, M. (2004). Sedative music reduces anxiety and pain during chair rest after open-heart surgery. *Pain, 112*(1), 197–203.

Wechsler, D. (1991). *Wechsler intelligence scale for children* (3rd ed.). San Antonio, TX: Psychological Corp.

White, E. J., Hutka, S. A., Williams, L. J., & Moreno, S. (2013). Learning, neural plasticity and sensitive periods: Implications for language acquisition, music training and transfer across the lifespan. *Frontiers in Systems Neuroscience, 7,* 90.

Woodward, J., & Sikes, P. L. (2015). The creative thinking ability of musicians and nonmusicians. *Psychology of Aesthetics, Creativity, and the Arts, 9*(1), 75.

Zatorre, R. J., Chen, J. L., & Penhune, V. B. (2007). When the brain plays music: Auditory–motor interactions in music perception and production. *Nature Reviews Neuroscience, 8*(7), 547–558.

Zuk, J., Benjamin, C., Kenyon, A., & Gaab, N. (2014). Behavioral and neural correlates of executive functioning in musicians and non-musicians. *PLoS One, 9*(6), e99868.


video
games

Video Games

Ronald Andringa and Walter R. Boot

Introduction

Whether or not certain mentally stimulating activities can improve cognition, enhancing our ability to perform important tasks in our everyday lives, is a controversial topic. In 2014, more than 70 scientists signed a consensus statement arguing that there is little or no compelling evidence that "brain games" can improve cognition (Stanford Center on Longevity 2014). A counter-consensus statement was released a few months later signed by 133 scientists and practitioners. While this counter statement acknowledged that many claims regarding the efficacy of brain training programs have been overstated by companies marketing products, it ultimately concluded that there is a solid and growing body of evidence in support of the effectiveness of some types of brain training, including commercial brain games currently on the market (Cognitive Training Data 2014). Consistent with the claim that the effectiveness of brain training programs is often exaggerated, the U.S. Federal Trade Commission recently fined Lumos Labs, maker of the brain training program Lumosity, $2 million for deceptive advertising (Federal Trade Commission 2016).

This chapter will focus on the evidence for one type of brain training that has received a great deal of attention, and appears to be one of the more promising routes to boosting cognition. Specifically, we examine the role video game training, utilizing commercially available games designed for entertainment purposes, might play in enhancing cognition. While initial findings are promising, the degree to which video game training transfers to other tasks and can improve the performance

R. Andringa · W.R. Boot (✉)
Department of Psychology, Florida State University,
1107 W. Call Street, Tallahassee, FL 32306-4301, USA
e-mail: boot@psy.fsu.edu

L.S. Colzato, *Theory-Driven Approaches to Cognitive Enhancement*,
DOI 10.1007/978-3-319-57505-6_14

of everyday tasks is debated. The aim of this chapter is to present the evidence for (and against) the idea that video game play can improve cognition, examine this evidence critically, and to present recommendations for more definitive tests of the potential relationship between gameplay and superior perceptual and cognitive abilities.

What Is a Video Game?

In the United States, 65% of households own a device used to play video games, and there are about two gamers in every U.S. household (Entertainment Software Association 2016). In 2015, video game-related sales reached $23.5 billion in the United States alone. With this medium rapidly proliferating across our technological, economic, cultural, and social landscape, it is not surprising that researchers have spent a great deal of time and effort trying to understand the possible positive and negative consequences of video game play.

Esposito (2005) provides a simple, short, and comprehensive video game definition: "A video game is a game in which we play thanks to an audio-visual apparatus (e.g., electronic computers, gaming consoles, mobile phones, interactive peripheral devices) and which can be based on a story." It is clear from this definition that it makes little sense to talk about the effects of "video game" play on something (e.g., cognition, aggression). What counts as a video game is far too broad to expect homogenous effects. Definitions of what a "game" is make it clear that games (including video games) are capable of varying along several important dimensions. Zimmerman (2004) defines a game as "a voluntary interactive activity in which one or more players follow rules that constrain their behavior, enacting artificial conflict that ends in a quantifiable outcome." Video games can differ in the degree and nature of player interactivity, the number of players, game rules, the specific behavior or set of behaviors of the player being constrained, and the nature of the conflict that must be overcome (and the skills necessary to do so). Based on the dimensions along which games can vary, video games can be organized into different genres based on gameplay (Konzack 2014). For example, action games typically require fast responses and place high demands on hand–eye coordination, with common subgenres including fighting games and first-person shooters, while strategy games are slower paced and involve components of planning and decision-making, and often involve play across a large map in which resources must be collected and allocated.

A great deal of research has specifically examined the potential effects of action video game play on perception and cognition, and this will be the primary focus of the current chapter. Within this literature, action games are "characterized by complex 3D settings, quickly moving and/or highly transient targets, strong peripheral processing demands, substantial amounts of clutter, and the need to consistently switch between highly focused and highly distributed attention, all while making rapid but accurate actions" (Green and Bavelier 2015). The most

commonly studied action video game subgenre is the first-person shooter. Common to these games, players must navigate 3D environments and shoot enemies while avoiding being shot (often with many enemies attacking at the same time). A number of published studies have found associations between the amount of action video game play a person engages in and their performance on tests of perceptual and cognitive abilities, and training studies that have asked people to play action games or non-action games have provided converging evidence that action video game play can improve these same abilities.

Evidence for Action Game Effects

In 1980s and 1990s, a number of studies were published finding a relationship between video game play and cognition, and a few training studies found that participants randomly assigned to play fast-paced video games improved more on perceptual and cognitive tests compared to participants who were not assigned to play video games (see Boot 2015; Simons et al. 2016). These studies often relied solely on non-experimental designs and experimental designs that did not include strong control groups (e.g., control groups that did not engage in some alternative activity). For these reasons they are not a major focus of the current chapter. However, in 2003 Shawn Green and Daphne Bavelier published an extremely influential paper in *Nature* that reinvigorated interest in the potential of video games as a tool for perceptual and cognitive enhancement (Green and Bavelier 2003). First, the performance of non-gamers (who reported minimal video game usage in the past 6 months) was compared to the performance of action video game players (who reported at least 1 h of action gameplay on 4 days per week over the past 6 months). Action gamers outperformed non-gamers on all reported measures of attentional breadth, flexibility, and capacity (as measured by classic laboratory paradigms including Useful Field of View (UFOV), attention blink, enumeration, and perceptual load tasks). In a separate study, non-gamers were randomly assigned to receive 10 h of experience playing *Tetris*, a puzzle game, or *Call of Duty*, an action video game. Action game assigned participants improved significantly more on the UFOV, attention blink, and enumeration tasks, providing evidence for a causal relationship between action gameplay and superior visual and attentional abilities. Results were notable because of the relatively strong control group (an active control group that played a different video game), the fact that improvements were observed after just 10 h of gameplay, and the fact that improvements were observed on the UFOV task, a task that correlates with automobile crash risk (Ball et al. 2005).

It was subsequently reported that action game training has the potential to improve visual acuity, contrast sensitivity, and the ability to track multiple fast-moving objects (e.g., Green and Bavelier 2006, 2007; Li et al. 2009). Many of these later studies report using significantly more game training, often ranging between 30 and 50 h. Action game effects do not appear to be restricted to visual

processing. At least two studies have demonstrated that action game training appears to improve the ability to keep two tasks in mind and rapidly switch between them (i.e., task switching ability; Green et al. 2012; Strobach et al. 2012). Studies comparing gamers and non-gamers have found similar effects (e.g., Colzato et al. 2010; Steenbergen et al. 2015). Another study has reported that action game training can improve visual short-term memory (Blacker et al. 2014), and action game experience is also associated with working memory benefits (Colzato et al. 2013). Action game-trained participants appear to be better able to quickly extract the information necessary to make accurate decisions (Green et al. 2010). Some have even suggested that action video game training can address the root causes of dyslexia in children (Franceschini et al. 2013). While a complete review of the action video game literature is beyond the scope of the current chapter, the reader can refer to Bavelier et al. (2012) and Green and Bavelier (2015) for a more detailed discussion.

Mechanisms of Action

A variety of mechanisms of action have been proposed linking action video game training to improvements in perceptual and cognitive performance. A "common demands" hypothesis claims that many different skills are exercised within action video games (Oei and Patterson 2015). Multiple objects (enemies) must be tracked simultaneously, targets must be detected in the periphery, and attention must be switched rapidly depending on the changing demands of the game environment. Practicing these skills in the varied contexts of action games repeatedly, often under time pressure, allows these skills to then transfer beyond the game itself. This view is in contrast to the proposed "learning to Learning to " hypothesis (Bavelier et al. 2012). This hypothesis claims that action video game experience enhances the ability to extract task-relevant information from the environment to learn new tasks. This is consistent with the finding of Bejjanki et al. (2014) that gamers initially show no advantage, but exhibit a more rapid rate of learning compared to non-gamers. This parsimonious explanation can account for the broad transfer observed to many different perceptual and cognitive outcome measures. While this explanation is appealing, it is also unsatisfying in some respects. It is still unclear from this account what the "active ingredient" is within action games that facilitates the ability to learn more rapidly. Finally, some accounts propose that instead of changing fundamental aspects of cognition, game experience may change how gamers approach tasks (i.e., strategy; Clark et al. 2011). Even short-term game exposure appears to influence whether individuals adopt a strategy prioritizing speed or accuracy (Nelson and Strachan 2009).

Understanding mechanisms of transfer may require a more detailed study of not just transfer task performance, but also game performance. Much might be gained by developing a more detailed understanding of what participants are doing and learning during gameplay (Towne et al. 2014, 2016). Process tracing approaches

such as verbal protocol analysis and eyetracking may help link performance changes within action games to performance changes within laboratory tasks of perception and cognition.

While initial evidence suggests that action game training can transfer to a number of other tasks, the mechanisms of this transfer are not well understood yet. Additionally, some researchers have questioned whether part or all of previously observed game effects may be due to methodological confounds. These critics have also suggested that game effects may not be as large and robust as initially thought. These criticisms have major implications for whether or not gaming interventions can be recommended as means to boost cognition.

Failures to Replicate

It is well known that null results are difficult to publish, and that in psychology, medicine, and other research domains there is an excess of positive findings in the literature (Francis 2012; Ioannidis 2005; Rosenthal 1979). Past and recent meta-analyses confirm that the video game literature is no exception. For example, a meta-analysis of cross-sectional game studies conducted by Powers et al. (2013) found that estimates of effect size were reduced from moderate-large to small when correcting for publication bias (see Ferguson 2007; for a similar, earlier finding). For game training studies, estimates of a small-medium effect were reduced to small when accounting for bias. These analyses suggest that if video game play does have an impact on perceptual and cognitive abilities, this effect may be smaller than initially thought.

Further, there have been failures to replicate studies finding an association between gameplay and cognition. Unsworth et al. (2015) examined the relationship between previous video game experience (including action video game experience) and a variety of cognitive abilities in samples of participants 10–20 times larger than the typical video game study (Study 1: $N = 252$; Study 2: $N = 586$). The authors explored the relationship between game experience and cognition at the latent construct level by having participants complete multiple tests tapping the domains of attentional control, working memory, and reasoning ability. In both studies, few robust relationships were observed between gameplay and cognition, and the few effects that were observed were small. Unsworth et al. (2015) ultimately conclude that that video game experience is weakly, if at all, associated with cognitive ability.

Additional cross-sectional studies have tried to replicate and extend previous findings of a gamer advantage. Donohue et al. (2012) conducted an experiment with the aim of exploring whether gamers might multitask better compared to non-gamers. Gamers and non-gamers played a racing game, performed a multiple object tracking task, and performed a visual search task, both under single-task and dual-task conditions. The dual-task condition involved also answering trivia questions. Not only did gamers fail to exhibit evidence of superior multitasking,

they failed to perform significantly better than non-gamers on the multiple object or visual search tasks under single-task conditions. Perhaps not surprisingly, habitual gamers outperformed non-gamers on the racing video game. Gaspar et al. (2014) similarly tested gamers and non-gamers in multitasking situations. In this case, participants had to cross a busy simulated roadway as a pedestrian under single- and dual-task load (a working memory task). Again, there was no relationship between multitasking performance and game experience, and there was also no difference between gamers and non-gamers on any of the other tests in a cognitive battery. Tests included measures of UFOV, visual short-term memory, and attentional control. Each of these has been found to be sensitive to game experience in the past.

Game training studies have also failed to find differences between action game training and non-action game training. Green et al. (2010) proposed that action game experience can speed visual information processing. Van Ravenzwaaij et al. (2014) tested this claim in two training studies (one involving 10 h of training, another 20 h). The outcome measure was a visual discrimination task in which participants had to detect coherent motion, a task very similar to the one used by Green et al. (2010). Participants either played the action game *Unreal Tournament* or the non-action game *The Sims*. Unlike the results of Green and colleagues, Van Ravenzwaaij et al. (2014) found no hint of an advantage for participants who played the action game.

Boot et al. (2008) conducted a fairly close replication of the original Green and Bavelier (2003) training study. Rather than 10 h, Boot and colleagues had participants train for 20 h, and also tested double the number of participants per condition compared to the original study. Despite increased training duration and statistical power, action game-trained participants did not improve more than non-action game-trained participants on any of the collected outcome measures, including measures of UFOV, multiple object tracking, visual short-term memory, and executive control.

Inconsistent findings might suggest that other factors may be important in determining whether or not game effects are observed (i.e., moderators). Cardoso-Leite et al. (2016) found little support for an action gamer advantage on four tasks that tapped attention and memory (i.e., few significant main effects of game experience). However, interactions were observed between game experience and the amount of media-multitasking participants engaged in. Media multitasking refers to the tendency to consume multiple forms of media simultaneously, such a reading a book and listening to music at the same time. Action gamers who were high and low media multitaskers exhibited no advantage over non-gamers. However, for intermediate media multitaskers, action gamers outperformed non-gamers.

Hartanto et al. (2016) report that the association between game experience and task switching performance may depend on the age an individual started actively playing video games. Switch costs, for example, did not differ significantly between non-gamers and active gamers who began playing after the age of 12, but did differ between non-gamers and gamers who began playing before the age of 12. On average, participants were 22 years of age, meaning 10 years of gameplay may be necessary before some associations between game play and cognition are observed.

If one assumes that there are indeed causal mechanisms at play, this has significant implications for using games to improve cognition.

Methodological Issues

A number of methodological issues have been raised calling the validity of studies linking gaming and cognition into question. Many studies simply report an association between the amount of gaming a person engages in and his or her perceptual and cognitive performance. Although this pattern is suggestive of the benefits of action video game play, directionality and third-variable problems prevent this evidence from being interpreted as providing a causal link (Boot et al. 2011; Boot and Simons 2012; Kristjánsson 2013). It has also been suggested that recruitment materials for these types of studies that highlight action game skill may bias gamers to be more motivated once they enter the laboratory. Participants know they are being sought for their expertise in fast-paced, visually demanding games, which may influence how they approach the fast-paced, visually demanding outcome measures researchers ask them to perform (but see Green et al. 2014; for a counterargument). However, these concerns appear to be partly justified as recruitment materials have been found to bias how participants perform in brain training studies (Foroughi et al. 2016).

While in principle, training studies allow for causal conclusions to be drawn regarding the efficacy of video game experience, the strength of the control group also needs to be considered. A proper control group adequately addresses the problem of placebo effects, which are observed improvements not due to the power of the intervention itself, but to participants' expectation that the intervention should work. "Sit-and-wait", or no-contact control groups that receive no treatment are insufficient to rule out placebo effects. It is unlikely that doing nothing will generate expectations of improvement as strong as doing something. Any video game training study that compares the effect of a video game to a control group that does nothing is obviously suspect. Active control groups, in which both the intervention group and the control group perform some type of task can better address the problem of placebo effects.

Recently, however, the idea that an active control group in and of itself is enough to control for placebo effects has been challenged. Boot et al. (2013) had participants view a video of a fast-paced action game (*Unreal Tournament*) or a slow-paced non-action game typically used as the control condition in gaming studies (*Tetris* or *The Sims*). Participants were then shown the most common cognitive measures used in these studies and asked about their expectation that the game they saw would improve performance on each cognitive task. Critically, expectations matched the outcome of game training studies in the literature perfectly. Since expectations matched the outcome of action game studies, Boot and colleagues interpreted this as action game effects being indistinguishable from

placebo effects. Unfortunately, few video game training studies at this point have measured or controlled for expectations (though see Blacker and Curby 2013).

Conclusion

In this chapter we have reviewed the growing body of evidence suggesting that action video game training is capable of improving perceptual and cognitive abilities. Action game training appears to be one of the most promising means of "brain training." However, we also raise a number of issues that need to be considered before definitive conclusions can be drawn. In addition to evidence that game effects are less robust than initially thought, it is important to note that almost no studies have examined video game transfer beyond abstract laboratory tasks. It is unclear if action game training might, for example, help someone avoid an automobile crash, or make better financial decisions. These are critical questions that need to be answered before game training can be recommended to anyone hoping to gain a cognitive edge.

Where do we go from here? Replication in science is crucial, thus large-scale replications of originally reported action game effects would be beneficial to the field. Larger samples (ideally, with 100 participants per condition or more) can help uncover whether individual difference factors might be important in moderating previously reported effects. These moderating effects might provide insight into previous failures to replicate game effects. Preregistration of intervention designs, outcomes, and analyses can boost confidence that results are robust and are not the result of selective reporting or p-hacking. Future studies might also measure expectations or manipulate expectations directly to help rule out placebo effects, and also assess potential benefits to important everyday tasks such as driving. Finally, a great deal might be learned by comparing game training conditions that are more similar. There are thousands of differences between an action game like *Call of Duty* and a puzzle game like *Tetris*. Any one of those differences might be crucial for producing game transfer effects. Game training studies that compare action game training to training *on the same game*, but with certain game elements removed, might help definitively link perceptual and cognitive improvements to an active ingredient within the action game.

References

Ball, K., Clay, O., Wadley, V., Roth, D., Edwards, J. D., & Roenker, D. L. (2005). Predicting driving performance in older adults with the useful field of view test: A meta-analysis. In *Proceedings of the Third International Driving Symposium on Human Factors in Driver Assessment, Training and Vehicle Design. Maine* (pp. 51–57).

Bavelier, D., Green, C. S., Pouget, A., & Schrater, P. (2012). Brain plasticity through the life span: Learning to learn and action video games. *Annual Review of Neuroscience, 35,* 391–416.

Bejjanki, V. R., Zhang, R., Li, R., Pouget, A., Green, C. S., Lu, Z. L., et al. (2014). Action video game play facilitates the development of better perceptual templates. *Proceedings of the National Academy of Sciences, 111*(47), 16961–16966.

Blacker, K. J., & Curby, K. M. (2013). Enhanced visual short-term memory in action video game players. *Attention, Perception, & Psychophysics, 75*(6), 1128–1136.

Blacker, K. J., Curby, K. M., Klobusicky, E., & Chein, J. M. (2014). Effects of action video game training on visual working memory. *Journal of Experimental Psychology: Human Perception and Performance, 40*(5), 1992.

Boot, W. R. (2015). Video games as tools to achieve insight into cognitive processes. *Frontiers in Psychology, 6*(3), 1–3.

Boot, W. R., Blakely, D. P., & Simons, D. J. (2011). Do action video games improve perception and cognition? *Frontiers in Psychology, 2*.

Boot, W. R., Kramer, A. F., Simons, D. J., Fabiani, M., & Gratton, G. (2008). The effects of video game playing on attention, memory, and executive control. *Acta Psychologica, 129*(3), 387–398.

Boot, W. R., & Simons, D. J. (2012). Advances in video game methods and reporting practices (but still room for improvement): A commentary on Strobach, Frensch, and Schubert (2012). *Acta Psychologica, 141*(2), 276–277.

Boot, W. R., Simons, D. J., Stothart, C., & Stutts, C. (2013). The pervasive problem with placebos in psychology: Why active control groups are not sufficient to rule out placebo effects. *Perspectives on Psychological Science, 8*(4), 445–454.

Cardoso-Leite, P., Kludt, R., Vignola, G., Ma, W. J., Green, C. S., & Bavelier, D. (2016). Technology consumption and cognitive control: Contrasting action video game experience with media multitasking. *Attention, Perception, & Psychophysics, 78*(1), 218–241.

Clark, K., Fleck, M. S., & Mitroff, S. R. (2011). Enhanced change detection performance reveals improved strategy use in avid action video game players. *Acta Psychologica, 136*(1), 67–72.

Cognitive Training Data. (2014). *An open letter to the stanford center on longevity*. http://www.cognitivetrainingdata.org/

Colzato, L. S., van den Wildenberg, W., Zmigrod, S., & Hommel, B. (2013). Action video gaming and cognitive control: Playing first person shooter games is associated with improvement in working memory but not action inhibition. *Psychological Research, 77,* 234–239.

Colzato, L. S., van Leeuwen, P. J. A., van den Wildenberg, W., & Hommel, B. (2010). DOOM'd to switch: Superior cognitive flexibility in players of first person shooter games. *Frontiers in Psychology, 1,* 8.

Donohue, S. E., James, B., Eslick, A. N., & Mitroff, S. R. (2012). Cognitive pitfall! Videogame players are not immune to dual-task costs. *Attention, Perception, & Psychophysics, 74*(5), 803–809.

Entertainment Software Association. (2016). *Essential facts about the computer and video game industry*. http://essentialfacts.theesa.com/Essential-Facts-2016.pdf.

Esposito, N. (2005). A short and simple definition of what a videogame is. In *Proceedings of the DiGRA 2005 Conference: Changing Views—Worlds in Play.*

Federal Trade Commission. (2016). *Press release*: *lumosity to pay $2 million to settle FTC deceptive advertising charges for its "brain training" program.* https://www.ftc.gov/news-events/press-releases/2016/01/lumosity-pay-2-million-settle-ftc-deceptive-advertising-charges

Ferguson, C. J. (2007). The good, the bad and the ugly: A meta-analytic review of positive and negative effects of violent video games. *Psychiatric Quarterly, 78*(4), 309–316.

Foroughi, C. K., Monfort, S. S., Paczynski, M., McKnight, P. E., & Greenwood, P. M. (2016). Placebo effects in cognitive training. In *Proceedings of the National Academy of Sciences*, 201601243.

Franceschini, S., Gori, S., Ruffino, M., Viola, S., Molteni, M., & Facoetti, A. (2013). Action video games make dyslexic children read better. *Current Biology, 23*(6), 462–466.

Francis, G. (2012). Too good to be true: Publication bias in two prominent studies from experimental psychology. *Psychonomic Bulletin & Review, 19*(2), 151–156.

Gaspar, J. G., Neider, M. B., Crowell, J. A., Lutz, A., Kaczmarski, H., & Kramer, A. F. (2014). Are gamers better crossers? An examination of action video game experience and dual task effects in a simulated street crossing task. *Human Factors: The Journal of the Human Factors and Ergonomics Society, 56*(3), 443–452.

Green, C. S., & Bavelier, D. (2003). Action video game modifies visual selective attention. *Nature, 423,* 534–537.

Green, C. S., & Bavelier, D. (2006). Enumeration versus multiple object tracking: the case of action video game players. *Cognition, 101,* 217–245.

Green, C. S., & Bavelier, D. (2007). Action video game experience alters the spatial resolution of attention. *Psychological Science, 18,* 88–94.

Green, C. S., & Bavelier, D. (2015). Action video game training for cognitive enhancement. *Current Opinion in Behavioral Sciences, 4,* 103–108.

Green, C. S., Pouget, A., & Bavelier, D. (2010). Improved probabilistic inference as a general learning mechanism with action video games. *Current Biology, 20*(17), 1573–1579.

Green, C. S., Strobach, T., & Schubert, T. (2014). On methodological standards in training and transfer experiments. *Psychological Research, 78*(6), 756–772.

Green, C. S., Sugarman, M. A., Medford, K., Klobusicky, E., & Bavelier, D. (2012). The effect of action video game experience on task-switching. *Computers in Human Behavior, 28*(3), 984–994.

Hartanto, A., Toh, W. X., & Yang, H. (2016). Age matters: The effect of onset age of video game play on task-switching abilities. *Attention, Perception, & Psychophysics, 78*(4), 1125–1136.

Ioannidis, J. P. (2005). Why most published research findings are false. *PLoS Medicine, 2*(8), e124.

Konzack, L. (2014). Video game genres. In *Encyclopedia of information science and technology* (3rd ed.). Hershey: IGI Global/Information Science Reference

Kristjánsson, Á. (2013). The case for causal influences of action videogame play upon vision and attention. *Attention, Perception, & Psychophysics, 75*(4), 667–672.

Li, R., Polat, U., Makous, W., & Bavelier, D. (2009). Enhancing the contrast sensitivity function through action video game training. *Nature Neuroscience, 12*(5), 549–551.

Nelson, R. A., & Strachan, I. (2009). Action and puzzle video games prime different speed/accuracy tradeoffs. *Perception, 38*(11), 1678–1687.

Oei, A. C., & Patterson, M. D. (2015). Enhancing perceptual and attentional skills requires common demands between the action video games and transfer tasks. *Frontiers in Psychology,* 6.

Powers, K. L., Brooks, P. J., Aldrich, N. J., Palladino, M. A., & Alfieri, L. (2013). Effects of video-game play on information processing: A meta-analytic investigation. *Psychonomic Bulletin & Review, 20*(6), 1055–1079.

Rosenthal, R. (1979). The file drawer problem and tolerance for null results. *Psychological Bulletin, 86*(3), 638–641.

Simons, D. J., Boot, W. R., Charness, N., Gathercole, S. E., Chabris, C. F., Hambrick, D. Z., et al. (2016). Do "brain-training" programs work? *Psychological Science in the Public Interest, 17*(3), 103–186.

Stanford Center on Longevity. (2014). *A consensus on the brain training industry from the scientific community*. http://longevity3.stanford.edu/blog/2014/10/15/the-consensus-on-the-brain-training-industry-from-the-scientific-community/

Steenbergen, L., Sellaro, R., Stock, A. K., Beste, C., & Colzato, L. S. (2015). Action video gaming and cognitive control: Playing first person shooter games is associated with improved action cascading but not inhibition. *PLoS One, 10*(12), e0144364.

Strobach, T., Frensch, P. A., & Schubert, T. (2012). Video game practice optimizes executive control skills in dual-task and task switching situations. *Acta Psychologica, 140*(1), 13–24.

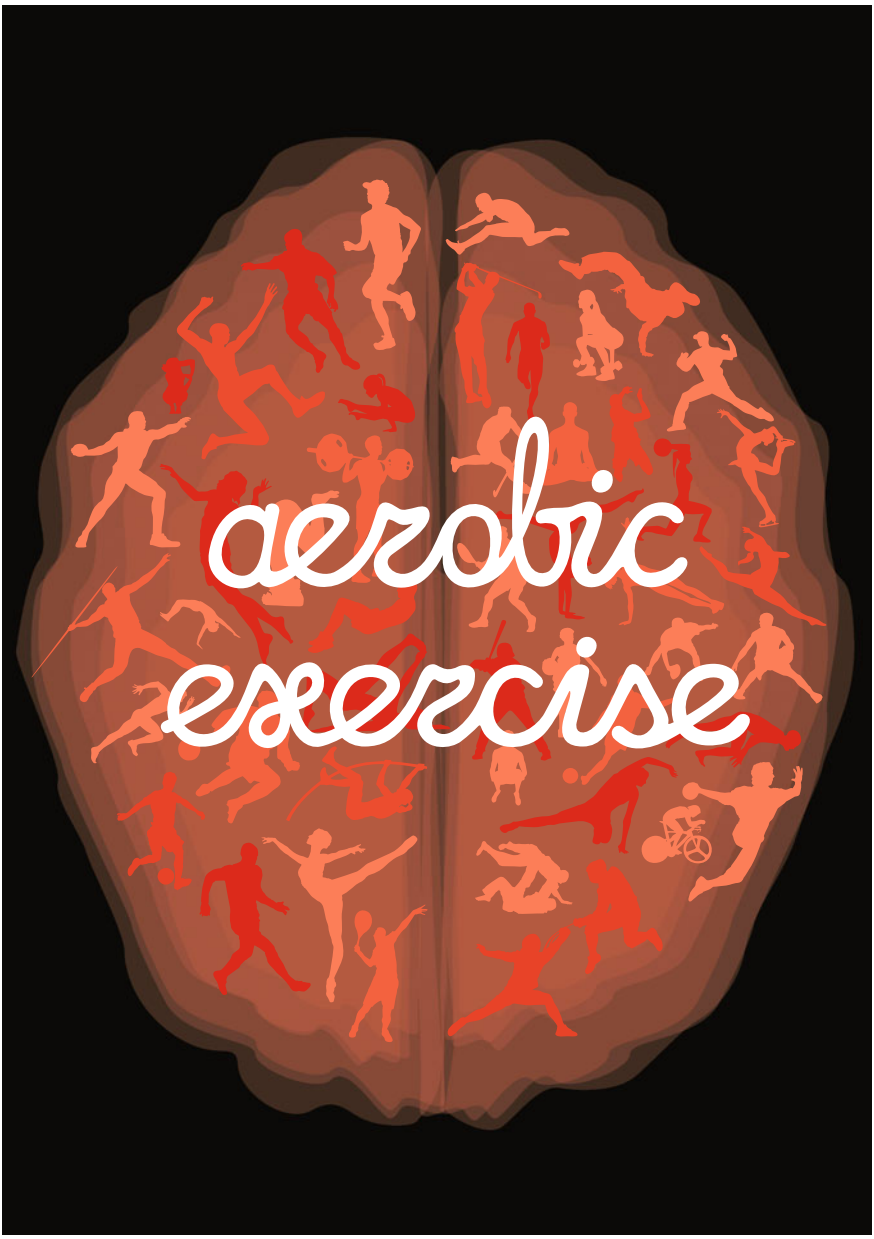
Towne, T. J., Boot, W. R., & Ericsson, K. A. (2016). Understanding the structure of skill through a detailed analysis of individuals' performance on the Space Fortress game. *Acta Psychologica, 169,* 27–37.

Towne, T. J., Ericsson, K. A., & Sumner, A. M. (2014). Uncovering mechanisms in video game research: Suggestions from the expert-performance approach. *Frontiers in Psychology, 5,* 161.

Unsworth, N., Redick, T. S., McMillan, B. D., Hambrick, D. Z., Kane, M. J., & Engle, R. W. (2015). Is playing video games related to cognitive abilities? *Psychological Science, 26*(6), 759–774.

van Ravenzwaaij, D., Boekel, W., Forstmann, B. U., Ratcliff, R., & Wagenmakers, E. J. (2014). Action video games do not improve the speed of information processing in simple perceptual tasks. *Journal of Experimental Psychology: General, 143*(5), 1794–1805.

Zimmerman, E. (2004). Narrative, interactivity, play, and games: Four naughty concepts in need of discipline. *First person: New Media As Story, Performance, and Game, 154.*


aerobic
exercise

Aerobic Exercise

Lorenza S. Colzato, Jonna Loeffler
and Rouwen Cañal-Bruland

Introduction

The interest in the influence of aerobic exercise on our daily life is constantly growing because of the enormous economic cost of sedentary lifestyle in western societies (Kruk 2014). The recommended guideline of at least 30 min of moderate-intensity physical activity on at least 5 days a week has not been met by one out of four adults worldwide, with a twice higher prevalence in high-income countries (33%) than in low-income countries (17%, World Health Organization 2014). Unfortunately, sedentary lifestyle has been reported to be associated with earlier onset of several chronic diseases such as diabetes and obesity, conditions responsible for the majority of medical costs associated with an inactive lifestyle (Kruk 2014). The prevalence of weight problems is increasing worldwide. There is growing evidence that high body mass index (BMI) is associated with frontal lobe dysfunction and cognitive deficits concerning memory processes (Cheke et al. 2016) and cognitive control or executive functions, that is, cognitive processes that

L.S. Colzato (✉)
Cognitive Psychology Unit and Leiden Institute for Brain and Cognition,
Leiden University, Leiden, The Netherlands
e-mail: colzato@fsw.leidenuniv.nl

L.S. Colzato
Institute of Cognitive Neuroscience, Faculty of Psychology,
Ruhr University Bochum, Bochum, Germany

J. Loeffler
Department Performance Psychology, Institute of Psychology,
German Sport University Cologne, Cologne, Germany

R. Cañal-Bruland
Institute of Sport Science, Friedrich-Schiller-University Jena, Jena, Germany

L.S. Colzato, *Theory-Driven Approaches to Cognitive Enhancement*,
DOI 10.1007/978-3-319-57505-6_15

are necessary for goal-directed thought and action, and mental flexibility (Sellaro et al. 2017).

Further, similar to meditation (see Chapter "Meditation"), aerobic exercise has been demonstrated to alleviate depression and anxiety (Carek et al. 2011), to promote positive feelings (Reed and Ones 2006) and to decrease stress (see, Heijnen et al. 2015, for a recent review on the topic). Besides the field of health care, in the past two decades the focus of scientific research has been shifted to the possible cognitive benefits that engaging in aerobic exercise may have on brain and cognition (for an early meta-analysis on the effects of exercise on cognitive function, see Etnier et al. 1997).

In this chapter we will first describe the neural mechanism underlying the mechanism of action through which aerobic exercise exerts its beneficial effect on cognition. Second, we will outline the available studies investigating aerobic exercise across the life span. The studies indicate that aerobic exercise has the potential to enhance cognition in children and compensates for cognitive decline in aging. Across the life span the largest fitness-induced benefits seem to occur for cognitive control processes. Finally, some considerations on the methodological limits of the research conducted so far and proposals for future studies will precede the general conclusions.

Mechanism of Action

The effects of aerobic exercise on cognition seem to be supported by a variety of brain processes including: increased hippocampal volume, increased gray matter density in the prefrontal cortex, upregulation of neurotrophins, and greater microvascular density (see, Voss et al. 2013, for a recent review on the topic). In specific, in this section we will elaborate on how aerobic exercise influences dopamine (DA), brain-derived neurotrophic factor (BDNF) and discuss a number of interindividual factors that affect their effects on cognition.

There is evidence suggesting that exercise-induced increment in DA and BDNF levels might be one of the key elements in explaining the beneficial effect of aerobic exercise on cognition. First, habitually physically active animals have been shown to be associated with enhanced ability to increase DA synthesis and reduce D2 autoreceptor-mediated inhibition of DA neurons compared to sedentary animals (see, Foley and Fleshner 2008, for a review on the effect of aerobic exercise on DA). This is particularly interesting given that DA seems to be responsible for the updating of knowledge and the choice of behavioral alternatives under changing situational conditions and demands (Cools 2006).

Second, BDNF seems to exert enhancing effects on cognition via its ability to enhance neurogenesis, synaptic plasticity and long-term potentiation, the basis of learning (Leckie et al. 2014). A recent review (Huang et al. 2014) concludes that a single session of aerobic exercise (intense running or cycling, ranging from 20 to 90 min) increases BDNF levels and that frequent aerobic training (moderate running or walking for elderly populations) boosts this rise. Along the same lines, a new

meta-analysis (Szuhany et al. 2015) on the effect of aerobic exercise on BDNF suggests similar conclusions, however, pointing out that, for women, the rise in BDNF was less robust. Further, a seminal recent study has shown that in a healthy elderly population (55–80 years old), moderate-intensity walking increased serum BDNF levels. This increment translated to a constant (not improved) task switching performance, whereas their sedentary peers' performance declined (Leckie et al. 2014).

Interestingly, BDNF increase after physical exercise has been found to be positively correlated with cognitive performance (Tsai et al. 2014). In particular, individuals with at least one Met allele on the Val66Met BDNF gene are associated with lower BDNF expression, smaller hippocampal volume and relatively low performance on memory tasks. These same carriers appear to have a more positive mood response to acute, moderate-intensity exercise (Hooper et al. 2014). This result is particularly interesting in suggesting that exercise may compensate for unfavorable genetic predispositions by reducing individual differences in memory functions. Furthermore, whereas Val homozygotes show a constant level of intrinsic motivation to exercise, people with at least one Met allele showed an increase of intrinsic motivation after an endurance training session (Hooper et al. 2014). In addition, they were more likely to continue exercising when they were told they could stop if they wanted. This points to an inverted u-shaped function where individuals with low baseline levels of BDNF seems to benefit relatively more from exercise as it boosts their BDNF levels up in the direction of the optimum. Hence, as pointed out by Heijnen et al. (2015), the efficiency of aerobic training programs and the beneficial effect on cognition might be modulated by interindividual differences, including pre-existing neurodevelopmental factors (e.g., Eggermont et al. 2006) and genetic differences (e.g., Hooper et al. 2014). Consequently, training programs that are tailored to individual abilities, skills, and needs might be more likely to succeed (see also Chapter "Theory-Driven Cognitive Enhancement: Costs and Benefits").

Exercise in Development: Enhancement in Children

In this section we will give an overview about recent findings investigating the effect of aerobic exercise on cognitive performance in children.

Aerobic fitness seems to have a small but positive association with academic achievement, whereas BMI has a negative association (Castelli et al. 2007). Along the same lines, a meta-analysis has pointed out to a positive relation between physical exercise and cognitive performance in school-age children (aged 4–18 years) in eight measurement categories (perceptual skills, intelligence quotient, achievement, verbal tests, mathematic tests, memory, developmental level/academic readiness and other, Sibley and Etnier 2003). In specific, more recent studies have shown that aerobic exercise, both following acute bouts and long-term aerobic training, promotes in particular cognitive control (see, Chang et al. 2012, for a recent review). First

evidence that aerobic exercise enhances cognitive control comes from Davis et al. (2007) in which overweight children (>85th percentile BMI, aged 7–11) completed an aerobic exercise intervention (15 weeks) involving group aerobic games (e.g., running games, modified basketball, and soccer). The study consisted of three treatment conditions: no exercise control, 20-min exercise dose or 40-min exercise dose. Aerobic training promoted only tasks requiring cognitive control and the improvement was dose–response dependent. Along the same lines, another study using a similar design revealed dose–response benefits of exercise on executive function and mathematics achievement (Davis et al. 2011). Further, a 9-month randomized controlled trial in prepubertal children attending an afterschool physical activity program (vs. a wait-list control group) revealed enhancements in fitness (Volume $Oxygen_{2peak}$), cognitive control, and electrical activity of the brain (P3-ERP) during tasks that necessitates a significant amount of cognitive control (Hillman et al. 2014). Also in the case of this study, a modest dose–response effect of program attendance predicted performance on cognitive control measures (Hillman et al. 2014).

Even though some studies following acute bouts of aerobic exercise have failed to find a beneficial effect of aerobic exercise on some facets of cognitive control (Tomporowski et al. 2008; Stroth et al. 2009), a seminal study by Hillman et al. (2009) revealed that acute treadmill walking promoted children's cognitive control. In a within-subject design children (mean age = 9.6 years) completed the Eriksen flanker task indexing response inhibition, both after 20 min of treadmill walking at moderate intensity and after 20 min of resting with no intervening activity. Aerobic exercise facilitated inhibitory control and the behavioral findings were highlighted by electrophysiological measurements of increased P3 amplitude located in frontocentral, central, and parietal regions. Along the same lines, Ellemberg and St. Louis-Deschênes (2010), in a between-group design, revealed that children who cycled for 40 min at a moderate intensity, compared to children who sat motionless on the stationary bike, displayed bigger enhancement in a task indexing cognitive control processes such as flexibility and inhibition compared to a simple reaction time task.

Interestingly, outcomes from research investigating the relationship between cognitive control and aerobic exercise in children show that poor performance on cognitive control tasks prospectively predict low levels of physical exercise (Riggs et al. 2010; Pentz and Riggs 2013). That is, as pointed out by Buckley et al. (2014), stronger cognitive control abilities are directly associated with augmented physical exercise behavior. Furthermore, in 9–10-year-old children, executive control proficiency was found to be negatively associated with sedentary behavior. This may indicate that a lack of cognitive capacity to plan exercise and/or to regulate may be one of the causes to inactivity (Riggs et al. 2010). Along the same lines, in a previous seminal study investigating undergraduate students, Hall et al. (2008) revealed that individual differences in cognitive control uniquely predict physical activity behavior. That is, greater baseline levels of inhibitory control, as indexed by better performance on a Go/NoGo task was related with the pattern of physical activity following a 7-day period.

In sum, the aforementioned studies are pointing out to the importance of aerobic exercise as a simple method of enhancing facets of children's mental functioning that are critical to cognitive development. Further, first studies show evidence (Pentz and Riggs 2013; Riggs et al. 2010) that the reported association between physical activity and cognitive functions is rather reciprocal than unidirectional.

Exercise in Elderly: Neuroprotective Factors in Aging

Human aging is accompanied by large decrements in cognitive control, which is not only particularly relevant for orchestrating adaptive behavior, but is also particularly sensitive and vulnerable. Cognitive control functions are the slowest to develop and assumed to be fully functional not much earlier than at 20 years of age, and they are the first to decay in normal aging (Gazzaniga 2004). One reason for this vulnerability is that cognitive control relies on the integrity of the frontal lobe, which is also known to mature rather late and to begin degenerating only a few years later. A related reason is the general loss of neurochemicals such as BDNF and DA (Bäckman et al. 2006; Lommatzsch et al. 2005). Considering the steady increase of elderly populations and the great importance of cognitive control functions for leading an independent, self-fulfilling life, it is crucial to understand how cognitive control can be promoted and, if possible, preserved in old age. Given that BDNF and DA decline in normal aging, a useful intervention for this purpose seems to be aerobic exercise. We suggest that aerobic exercise, aimed at increasing BDNF and DA levels, is likely to slow down, and (partially) compensate for the negative consequences associated with the loss of dopaminergic and BDNF supplies in aging. Indeed, a meta-analytic study (Colcombe and Kramer 2003; for a review along the same lines, see McAuley et al. 2004) has shown that fitness training was found to have robust but selective benefits for cognition, with the largest fitness-induced benefits occurring for cognitive control processes (which include scheduling, planning, working memory, multitasking, and dealing with ambiguity), if the intervention involved a significant dose of aerobic exercise and lasted over 6 months. Another study has shown that 3 months of supervised aerobic exercise was enough to induce significant enhancement in attention and cognitive control functions (Renaud et al. 2010).

Notably, the beneficial effect of aerobic exercise does not seem to be limited to healthy aging but also to frail older adults. After a 3-month exercise program, which consisted of combined aerobic and strength training exercise, moderately frail older adults exhibited enhanced physical functions together with improved speed of processing, executive control, and working memory (Langlois et al. 2013). Furthermore, a meta-analysis considering more than 30,000 participants worldwide pointed out to a decreased risk factor for dementia of up to 38% for the older adults engaged in moderately intense exercise more than three times per week (Sofi et al. 2011).

Interestingly, similarly to children, in a multiwave longitudinal study exploring the reciprocal relationship between cognitive control and physical activity in 4555 older adults (Daly et al. 2014), outcomes revealed that changes in cognitive control corresponded with changes in physical activity. Hence, high levels of cognitive control predicted a longitudinal increase in aerobic exercise. Furthermore, McAuley et al. (2011) investigated the relationship of cognitive control, self-regulation, and self-efficacy in compliance to a 12-month exercise intervention for older adults. Interestingly, at the begin of the exercise intervention, higher levels of cognitive control to coordinate tasks and inhibit habitual responses in conjunction with superior use of self-regulatory strategies were connected with higher levels of exercise self-efficacy. At the same time, higher self-efficacy was associated to superior compliance to weekly aerobic exercise during the intervention program. The outcomes of this study points out that at the beginning of a physical activity program, higher cognitive control skills are directionally linked to increased physical activity behavior. Although most of the studies show a positive relationship between cognitive control and physical activities in older adults, also contradictory results exist. For example, it is reported that older adults with poorer executive control were more likely to engage in self-regulated cycling (Anderson-Hanley et al. 2014). In sum, aerobic exercise, via its neuroprotective functions, seems to show promising potential to compensate for cognitive decline in aging. In addition, the association between cognitive control and aerobic exercise is reported to be reciprocal—higher cognitive control appears to be positively associated with the amount of self-regulated aerobic exercise in older adults.

Conclusion

All in all, the studies reviewed in this chapter suggest that aerobic exercise promotes cognitive enhancement in children and compensates for cognitive decline in aging. Across the life span the largest fitness-induced benefits seem to occur for cognitive control processes. For both, children and older adults, there seems to be a bidirectional relation between aerobic exercise and cognitive control: aerobic exercise fosters cognitive control, but at the same time, it is the baseline individual level of cognitive control which determines the capacity to plan exercise and/or to regulate needs to remain inactive (Buckley et al. 2014; Mullen and Hall 2015). Accordingly, future studies investigating the beneficial effects of aerobic exercise on cognition need to consider interindividual differences in cognitive control more systematically. Moreover, if aerobic exercise really affects neuroplasticity, it makes sense to assume that the effect of aerobic exercise on performance depends on the pre-experimental performance level of the individual—be it in terms of compensation (so that worse performers benefit more) or predisposition (so that some are more responsive to aerobic exercise interventions). Dealing with this matter will necessitate (more) longitudinal studies. Further, since efficacy of aerobic exercise may depend on various factors, among which genetic variability is related to

BDNF, we suggest taking into account such interindividual variability and tailoring exercise to individual needs will be crucial for developing successful endurance programs in the future.

Last, as suggested by Bherer (2015), a crucial question for future studies will be whether exercise interventions can be combined with cognitive training programs or other programs, such as meditation or nutrition, to further promote cognitive functions in older adults (for an example of a personalized, nondrug therapeutic program for patients with decreased memory performance, see Bredesen 2014). The idea is that by combining multiple training programs it may be possible to achieve synergetic effects of the combined intervention.

In sum, this chapter points out that across the life span engaging in aerobic exercise may be a valuable approach to promote facets of children's mental functioning that are critical to cognitive development and to counteract the deteriorative effect of aging on cognitive functioning.

References

Anderson-Hanley, C., Arciero, P. J., Barcelos, N., Nimon, J., Rocha, T., Thurin, M., et al. (2014). Executive function and self-regulated exergaming adherence among older adults. *Frontiers in Human Neuroscience, 8,* 989.

Bäckman, L., Nyberg, L., Lindenberger, U., Li, S.-C., & Farde, L. (2006). The correlative triad among aging, dopamine, and cognition: Current status and future prospects. *Neuroscience and Biobehavioral Reviews, 30,* 791–807.

Bherer, L. (2015). Cognitive plasticity in older adults: Effects of cognitive training and physical exercise. *Annals of the New York Academy of Sciences, 1337*(1), 1–6.

Bredesen, D. E. (2014). Reversal of cognitive decline: A novel therapeutic program. *Aging, 6*(9), 707–717.

Buckley, J., Cohen, J. D., Kramer, A. F., McAuley, E., & Mullen, S. P. (2014). Cognitive control in the self-regulation of physical activity and sedentary behavior. *Frontiers in Human Neuroscience, 8,* 747.

Carek, P. J., Laibstain, S. E., & Carek, S. M. (2011). Exercise for the treatment of depression and anxiety. *International Journal of Psychiatry in Medicine, 41*(1), 15–28.

Castelli, D. M., Hillman, C. H., Buck, S. M., & Erwin, H. E. (2007). Physical fitness and academic achievement in third-and fifth-grade students. *Journal of Sport and Exercise Psychology, 29*(2), 239.

Chang, Y. K., Labban, J. D., Gapin, J. I., & Etnier, J. L. (2012). The effects of acute exercise on cognitive performance: A meta-analysis. *Brain Research, 1453,* 87–101.

Cheke, L. G., Simons, J. S., & Clayton, N. S. (2016). Higher body mass index is associated with episodic memory deficits in young adults. *The Quarterly Journal of Experimental Psychology, 69*(11), 2305–2316.

Colcombe, S., & Kramer, A. F. (2003). Fitness effects on the cognitive function of older adults—A meta-analytic study. *Psychological Science, 14*(2), 125–130.

Cools, R. (2006). Dopaminergic modulation of cognitive function—Implication for L-DOPA therapy in Parkinson's disease. *Neuroscience and Biobehavioral Reviews, 30,* 1–34.

Daly, M., McMinn, D., & Allan, J. L. (2014). A bidirectional relationship between physical activity and executive function in older adults. *Frontiers in Human Neuroscience*. doi:10.3389/fnhum.2014.01044

Davis, C. L., Tomporowski, P. D., Boyle, C. A., Waller, J. L., Miller, P. H., Naglieri, J. A., et al. (2007). Effects of aerobic exercise on overweight children's cognitive functioning: A randomized controlled trial. *Research Quarterly for Exercise and Sport, 78*(5), 510–519.

Davis, C. L., Tomporowski, P. D., McDowell, J. E., Austin, B. P., Miller, P. H., Yanasak, N. E., et al. (2011). Exercise improves executive function and achievement and alters brain activation in overweight children: A randomized, controlled trial. *Health Psychology, 30*(1), 91.

Eggermont, L., Swaab, D., Luiten, P., & Scherder, E. (2006). Exercise, cognition and Alzheimer's disease: More is not necessarily better. *Neuroscience and Biobehavioral Reviews, 30*(4), 562–575. doi:10.1016/j.neubiorev.2005.10.004

Ellemberg, D., & StLouis-Deschênes, M. (2010). The effect of acute physical activity on cognitive function during development. *Psychology of Sport and Exercise, 11,* 122–126.

Etnier, J. L., Salazar, W., Landers, D. M., Petruzzello, S. J., Han, M., & Nowell, P. (1997). The influence of physical fitness and exercise upon cognitive functioning: A meta-analysis. *Journal of Sport and Exercise Psychology, 19,* 249–277.

Foley, T. E., & Fleshner, M. (2008). Neuroplasticity of dopamine circuits after exercise: Implications for central fatigue. *NeuroMolecular Medicine, 10*(2), 67–80.

Gazzaniga, M. S. (Ed.). (2004). *The Cognitive Neurosciences III* (3rd ed.). Cambridge, MA: A Bradford Book.

Hall, P. A., Fong, G. T., Epp, L. J., & Elias, L. J. (2008). Executive function moderates the intention-behavior link for physical activity and dietary behavior. *Psychology and Health, 23* (3), 309–326.

Heijnen, S., Hommel, B., Kibele, A., & Colzato, L. S. (2015). Neuromodulation of aerobic exercise: A review. *Frontiers in Psychology, 6,* 1890.

Hillman, C. H., Pontifex, M. B., Raine, L. B., Castelli, D. M., Hall, E. E., & Kramer, A. F. (2009). The effect of acute treadmill walking on cognitive control and academic achievement in preadolescent children. *Neuroscience, 3,* 1044–1054.

Hillman, C. H., Pontifex, M. B., Castelli, D. M., Khan, N. A., Raine, L. B., Scudder, M. R., et al. (2014). Effects of the FITKids randomized controlled trial on executive control and brain function. *Pediatrics, 134*(4), 1063–1071.

Hooper, A. E. C., Bryan, A. D., & Hagger, M. S. (2014). What keeps a body moving? The brain-derived neurotrophic factor val66met polymorphism and intrinsic motivation to exercise in humans. *Journal of Behavioral Medicine, 37*(6), 1180–1192.

Huang, T., Larsen, K. T., Ried-Larsen, M., Møller, N. C., & Andersen, L. B. (2014). The effects of physical activity and exercise on brain-derived neurotrophic factor in healthy humans: A review. *Scandinavian Journal of Medicine and Science in Sports, 24*(1), 1–10.

Kruk, J. (2014). Health and economic costs of physical inactivity. *Asian Pacific Journal of Cancer Prevention: APJCP, 15*(18), 7499–7503.

Langlois, F., Vu, T. T. M., Chassé, K., Dupuis, G., Kergoat, M. J., & Bherer, L. (2013). Benefits of physical exercise training on cognition and quality of life in frail older adults. *The Journals of Gerontology Series B: Psychological Sciences and Social Sciences, 68,* 400–404.

Leckie, R. L., Oberlin, L. E., Voss, M. W., Prakash, R. S., Szabo-Reed, A., Chaddock-Heyman, L., et al. (2014). BDNF mediates improvements in executive function following a 1-year exercise intervention. *Frontiers in Human Neuroscience*. doi:10.3389/fnhum.2014.00985

Lommatzsch, M., Zingler, D., Schuhbaeck, K., Schloetcke, K., Zingler, C., Schuff-Werner, P., et al. (2005). The impact of age, weight and gender on BDNF levels in human platelets and plasma. *Neurobiology of Aging, 26*(1), 115–123.

McAuley, E., Kramer, A. F., & Colcombe, S. J. (2004). Cardiovascular fitness and neurocognitive function in older adults: A brief review. *Brain, Behavior, and Immunity, 18,* 214–220.

McAuley, E., Mullen, S. P., Szabo, A. N., White, S. M., Wójcicki, T. R., Mailey, E. L., et al. (2011). Self-regulatory processes and exercise adherence in older adults: Executive function and self-efficacy effects. *American Journal of Preventive Medicine, 41*(3), 284–290.

Mullen, S. P., & Hall, P. A. (2015). Editorial: Physical activity, self-regulation, and executive control across the lifespan. *Frontiers in Human Neuroscience, 9,* 614. doi:10.3389/fnhum.2015.00614

Pentz, M. A., & Riggs, N. R. (2013). Longitudinal relationships of executive cognitive function and parent influence to child substance use and physical activity. *Prevention Science, 14*(3), 229–237.

Reed, J., & Ones, D. S. (2006). The effect of acute aerobic exercise on positive activated affect: A meta-analysis. *Psychology of Sport and Exercise, 7*(5), 477–514.

Renaud, M., Maquestiaux, F., Joncas, S., Kergoat, M. J., & Bherer, L. (2010). The effect of three months of aerobic training on response preparation in older adults. *Frontiers in Aging Neuroscience, 2,* 148.

Riggs, N., Chou, C. P., Spruijt-Metz, D., & Pentz, M. A. (2010). Executive cognitive function as a correlate and predictor of child food intake and physical activity. *Child Neuropsychology, 16*(3), 279–292.

Sellaro, R., & Colzato, L. S. (2017). High body mass index is associated with impaired cognitive control. *Appetite, 113*, 301–309.

Sibley, B. A., & Etnier, J. L. (2003). The relationship between physical activity and cognition in children: A meta-analysis. *Pediatric Exercise Science, 15*(3), 243–256.

Sofi, F., Valecchi, D., Bacci, D., Abbate, R., Gensini, G. F., Casini, A., et al. (2011). Physical activity and risk of cognitive decline: A meta-analysis of prospective studies. *Journal of Internal Medicine, 269*(1), 107–117.

Stroth, S., Kubesch, S., Dieterle, K., Ruchsow, M., Heim, R., & Kiefer, M. (2009). Physical fitness, but not acute exercise modulates event-related potential indices for executive control in healthy adolescents. *Brain Research, 1269,* 114–124.

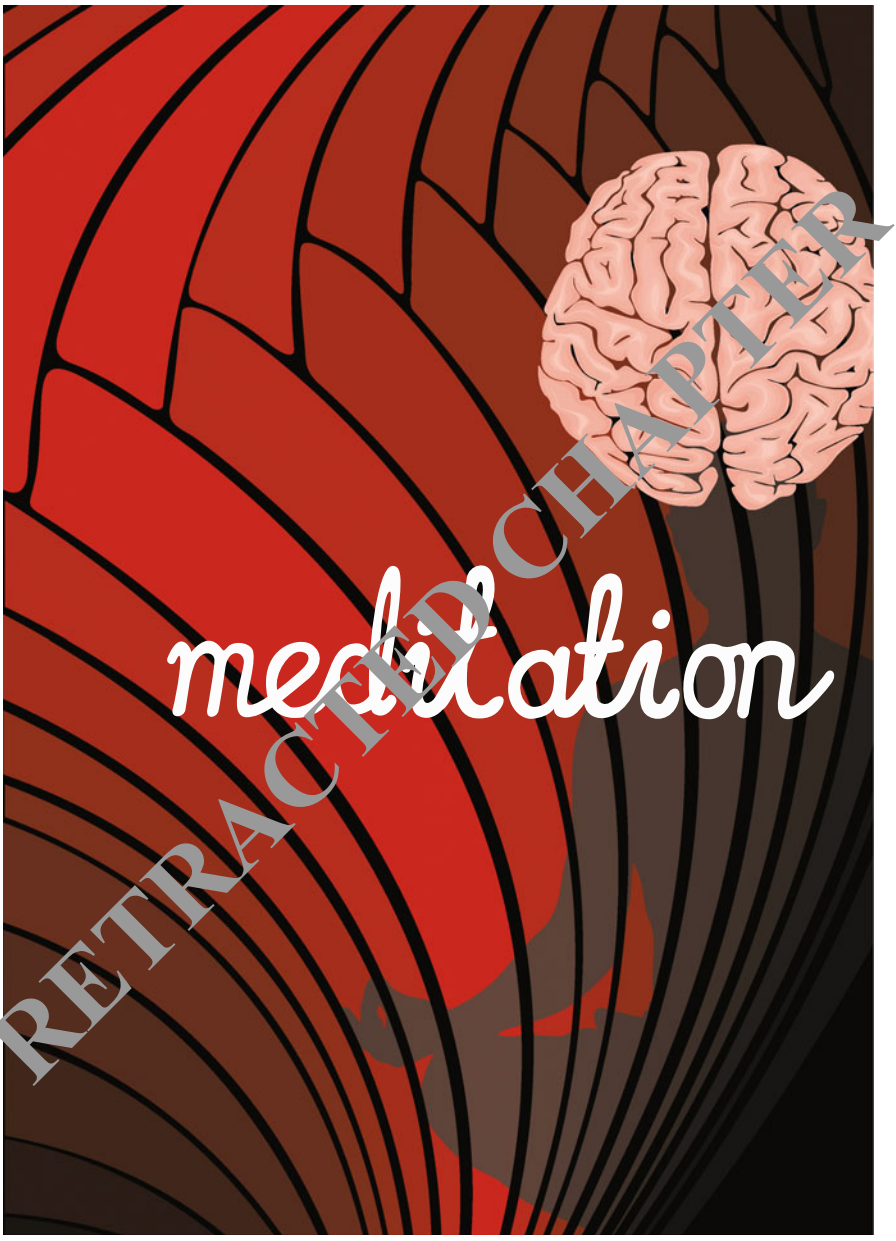
Szuhany, K. L., Bugatti, M., & Otto, M. W. (2015). A meta-analytic review of the effects of exercise on brain-derived neurotrophic factor. *Journal of Psychiatric Research, 60,* 56–64.

Tomporowski, P. D., Davis, C. L., Lambourne, K., Gregoski, M., & Tkacz, J. (2008). Task switching in overweight children: Effects of acute exercise and age. *Journal of Sport & Exercise Psychology, 30,* 497–511.

Tsai, C. L., Chen, F. C., Pan, C. Y., Wang, C. H., Huang, T. H., & Chen, T. C. (2014). Impact of acute aerobic exercise and cardiorespiratory fitness on visuospatial attention performance and serum BDNF levels. *Psychoneuroendocrinology, 41,* 121–131.

Voss, M. W., Vivar, C., Kramer, A. F., & van Praag, H. (2013). Bridging animal and human models of exercise-induced brain plasticity. *Trends in Cognitive Sciences, 17*(10), 525–544.

World Health Organization. (2014). *Global status report on noncommunicable diseases*. Geneva: World Health Organization.



RETRACTED CHAPTER: Meditation

Lorenza S. Colzato and Bernhard Hommel

Introduction

Since the 60s and 70s the practice of meditation has seen a remarkable increase in the western societies (Murphy and Donavon 1997). Scientific interest in meditation has also significantly increased in the past years (Cahn and Polich 2006) and growing evidence points to the potential use of meditation in health care and the field of stress management (Chiesa and Seretti 2009). Moreover, meditation has been found to be effective in increasing pain tolerance (Wachholtz and Pargament 2005), reducing anxiety (Crescentini et al. 2016b), and enhancing psychological well-being in primary school children (Crescentini et al. 2016a) and shaping individuals' personality and self-concept toward more healthy profiles (Crescentini and Capurso 2015). Thus, meditation seems to be an effective tool for enhancing general well-being. Whereas in the past meditation has been viewed as a technique primarily intended for relaxation and stress reduction, in recent years it has been demonstrated that meditation has significant enhancing effects on how people perceive and process the world around them and alter the way they regulate attention and emotion. In their seminal work Lutz et al. (2008) were the first to point out that two prototypes of meditation are commonly investigated: focused attention meditation (FAM) and open monitoring meditation (OMM). Whereas FAM requires the voluntary focusing of attention on a chosen object, OMM involves an overt, but unreactive, monitoring of the content of experience from moment to

The original version of this chapter was retracted: The retraction note to this chapter is available at https://doi.org/10.1007/978-3-319-57505-6_24

L.S. Colzato (✉) · B. Hommel
Cognitive Psychology Unit and Leiden Institute for Brain and Cognition, Leiden University, Leiden, The Netherlands
e-mail: colzato@fsw.leidenuniv.nl

L.S. Colzato
Faculty of Psychology, Institute of Cognitive Neuroscience, Ruhr University Bochum, Bochum, Germany

L.S. Colzato, *Theory-Driven Approaches to Cognitive Enhancement*,
https://doi.org/10.1007/978-3-319-57505-6_16

moment (Lutz et al. 2008). In line with the idea that different kinds of meditation affect human cognition in different ways, a recent meta-analysis concluded that different practices of meditation are indeed subserved by largely, if not entirely, disparate brain networks (Tomasino et al. 2013).

In this chapter, adapted from Lippelt et al. (2014), we will first describe how FAM and OMM, are likely to exert different, to some degree even opposite effects on cognitive (control) processes. Second, we will outline the available studies investigating the differential effect of FAM and OMM on attention and conflict monitoring. Third, we will review studies exploring the enhancing effects of meditation types on creativity processes. The studies indicate that the effect of FAM and OMM are not equal and that the potential to enhance cognitive processes depends on the theoretically guided selection of the best-suited technique.

Mechanism of Action: FAM Versus OMM

Commonly, FAM is the starting point for any novice meditator (Lutz et al. 2008; Vago and Silbersweig 2012). During FAM the practitioner is required to focus attention on a chosen object or event, such as breathing or a candle flame. To maintain this focus, the practitioner has to constantly monitor the concentration on the chosen event so to avoid mind wandering (Tops et al. 2014). After practitioners get acquainted with the FAM technique and can easily sustain their attentional focus on an object for a considerable amount of time, they often advance to OMM. During OMM the focus of the meditation becomes the monitoring of awareness itself (Lutz et al. 2008; Vago and Silbersweig 2012). In contrast to FAM, there is no object or event in the internal or external environment that the meditator has to focus on. The goal of OMM is rather to stay in the monitoring state, remaining attentive to any experience that might arise, without selecting, judging, or focusing on any particular object. To start, however, the meditator will focus on a chosen object, as in FAM, but will subsequently gradually reduce this focus, while emphasizing the activity of monitoring of awareness.

We argue that practicing tasks and skills such as meditation might establish chronic biases of cognitive control toward states or state parameters that these tasks and skills require. We propose that FAM increases top-down control and thus strengthens top-down support for relevant information and/or local competition between relevant and irrelevant information (Duncan 2001), while OMM weakens top-down control and thus reduces top-down support and/or local competition. Figure 1 captures the emerging idea that FAM tends to strengthen the impact of the task goal and/or the competition between alternatives (cf. Hommel 2015) by supporting parallel processing whereas OMM tends to weaken the impact of the task goal and/or the competition between alternatives (cf. Hommel 2015) by supporting serial processing.

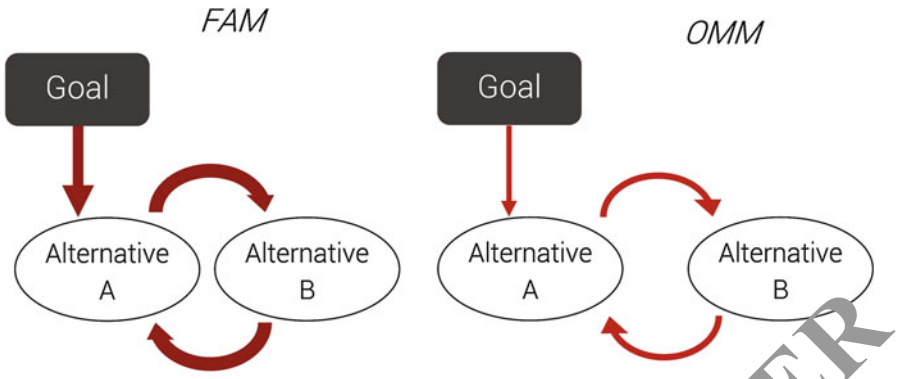


Fig. 1 Hypothetical impact of meditation-induced control states on the cognition. Focused attention meditation (FAM) is assumed to increase the impact of the task goal on goal-relevant information and/or the competition between alternative aspects of a stimulus by supporting serial processing. Open monitoring meditation (OMM) is assumed to weaken the impact of the goal and/or mutual competition by supporting parallel processing

Enhancing Effect on Attention

In a seminal study, Slagter et al. (2007) investigated the effects of 3 months of intensive Vipassana meditation (an OMM-like meditation) training on the allocation of attention over time as indexed by the "attentional blink (AB)" deficit, thought to result from competition between two target stimuli (T1 and T2) for limited attentional resources. After the training participants showed a smaller AB deficit as an indication of being able to distribute their brain resource allocation to both T1 and T2. The reduced AB size was accompanied by a smaller T1-elicited P3b, a brain potential thought to index attentional resource allocation. Van Leeuwen et al. (2009) found age-(and/or practice-) related effects of long-term meditation. In line with these results, only the older and very experienced meditators (on average 10,704 h of experience) showed a smaller AB during OMM than during FAM (van Vugt and Slagter 2014). Notably, in non-meditators a brief single bouts of either FAM or OMM was enough to impact efficiency of allocating attention over time: the size of the AB was considerably smaller after OMM than after FAM, which suggests that engaging in meditation creates a cognitive control state that has a specific impact on how people allocate their attention over time (Colzato et al. 2015a). Indeed, OMM induces a more parallel processing style by weakening top-down support for relevant information and/or reducing local competition between relevant and irrelevant information (Lippelt et al. 2014; Colzato et al. 2015b), while FAM has the opposite effect. This would be expected to lead to a broader distribution of attention over time after OMM and, thus, a smaller AB—just as the findings above demonstrated (Slagter et al. 2007; van Leeuwen et al. 2009; van Vugt and Slagter 2014).

Another study comparing meditators (trained in mindfulness-based stress reduction) to non-meditators found that meditators show evidence of more accurate and efficient visual attention (Hodgins and Adair 2010). Meditators monitored events more accurately in a concentration task and showed less interference from invalid cues in a visual selective attention task. Furthermore, meditators showed improved flexible visual attention by identifying a greater number of alternative perspectives in multiple perspectives images. Further, a study compared OMM and FAM meditators on a sustained attention task (Valentine and Sweet 1999): OMM meditators outperformed FAM meditators when the target stimulus was unexpected. This might indicate that the OMM meditators could be associated with a wider attentional scope, even though the two meditator groups did not differ in performance when the stimulus was expected. However this idea has been challenged by the outcome that long-term practice does not seem to affect the global precedence effect (i.e., performance is better when responding to global than to local features; Chan and Woollacott 2007). This is a notable outcome given that global precedence is supposed to reflect a bias toward a large, comprehensive attentional focus, while attending to local features is considered to require more effort. A recent study replicated the outcome by Chan and Woollacott (2007) in finding no indication that the global precedence effect would be affected by a single bout of meditation in non-meditators (Colzato et al. 2015b). Given that global precedence reflects attentional spatial focusing whereas the AB is considered an index of attentional temporal focusing, it seems that meditation alters the latter (Slagter et al. 2007; van Leeuwen et al. 2009; van Vugt and Slagter 2014) but not the former (Chan and Woollacott 2007; Colzato et al. 2015b).

Electrophysiological evidence for meditation-induced enhancement in attention comes from a recent study in which Vipassana meditators performed an auditory oddball task before and after meditation (in one session) and random thinking (in another session) (Delgado-Pastor et al. 2013). Meditators showed greater P3b amplitudes to target tones after meditation than either before meditation or after the no-meditation session, an effect that is thought to reflect enhanced attentional engagement during the task.

Evidence for the assumption that FAM strengthens top-down support by supporting serial processing comes from several studies that show that FAM increases sustained attention (Carter et al. 2005; Brefczynski-Lewis et al. 2007). Neuroimaging evidence by Hasenkamp et al. (2012b) suggests that FAM is associated with increased activity in the right dorsolateral prefrontal cortex (DLPFC), which has been associated with "the repetitive selection of relevant representations or recurrent direction of attention to those items" (D'Esposito 2007, p. 765) 2012. Thus, in the context of meditation experience, DLPFC might be involved in repeatedly redirecting or sustaining attention to the object of focus. It would be interesting to investigate whether this pattern of activation is unique to FAM or whether OMM leads to similar increases in activity in the DLPFC. If the DLPFC is indeed involved in the repetitive redirection of attention to the same object of focus, then it should not be as active during OMM during which attention is more flexible and continuously shifted to different objects. Alternatively, however, if during

OMM the meditator achieves a state of awareness where (only) awareness itself is the object of focus, the DLPFC might again play a role in maintaining this focus.

In a follow-up study, Hasenkamp and Barsalou (2012a) found that, during rest, the right DLPFC connectivity to the right insula was improved in experienced meditators compared to novices. The authors suggest that improved connectivity with the right insula might reflect enhanced interoceptive attention to internal bodily states. In line with this idea, a recent study reports that mindfulness training predicted greater activity in posterior insula regions during interoceptive attention to respiratory sensation (Farb et al. 2013). Various studies have shown theta activity to be increased during meditation, primarily OMM-like meditations (e.g., Baijal and Srinivasan 2010; Cahn et al. 2010; Tsai et al. 2013; for review see Travis and Shear 2010). This increase in theta activity, usually mid-frontal, has been suggested to be involved in sustaining internalized attention. As such, similar increases in theta activity would not be expected during FAM where attention is explicitly focused on an external object, even though typically the object of meditation in FAM, at least for beginners, is the breath, which is internal.

In sum, because FAM and OMM support serial and parallel processing respectively, see Fig. 1, they show differential enhancing effect on attention: OMM leads to a broader distribution of attention over time, whereas FAM supports sustained attention.

Enhancing Effect on Conflict Monitoring

A fundamental skill acquired through meditation is the ability to monitor the attentional focus in order to "redirect it" in the case of conflicting thoughts or external events. Not surprisingly, several studies have already shown enhancement in conflict monitoring after meditation.

In a seminal study, Tang et al. (2007) investigated whether a training technique based on meditational practices called integrative body–mind training could improve performance on an Attentional Network Task (Fan et al. 2002). This paradigm is based on a flanker task and was developed to keep track of three different attentional subskills: orientation, alerting, and conflict resolution. In the flanker task, participants discriminate a single target (e.g., letter or arrow) that is surrounded, or flanked, by distractors that indicate the same or opposite response (Eriksen and Eriksen 1974). While integrative body–mind training had no effect on orienting and alerting scores, it did improve conflict resolution.

A new study, implying the Simon task, investigated the differential effect of FAM and OMM on the so-called "conflict adaptation effect" (aka Gratton effect). The Gratton effect has been taken to reflect the increase of cognitive control triggered by the experience of conflict (Botvinick et al. 2001). The amount of dynamic behavioral adjustments (i.e., trial-to-trial variability of the Simon effect as indexed by the Gratton effect) was considerably smaller after OMM than after FAM (Colzato et al. 2015b). Notably, the Gratton effect is an index of control fluctuation

and resulting adaptation and seems to rely on a regulatory feedback involving the anterior cingulate cortex (ACC) and the medial prefrontal cortex (PFC) (Botvinick 2007; Botvinick et al. 1999, 2004), the same brain areas found to be associated with enhanced cerebral blood flow with 5 days (30-min per day) integrative body–mind training (Tang et al. 2015). Along the same lines, another study in which meditation-naïve participants were randomly assigned to either an 11 h integrative body–mind training course or a relaxation training, has reported that the integrative body–mind training group showed higher network efficiency and degree of connectivity of the ACC than a group that underwent relaxation training, (Xue et al. 2011). Moreover, several other studies have also shown improvements in ACC functioning after meditation (Lazar et al. 2000; Bærentsen et al. 2001; Tang et al. 2009, 2010). Given that both meditation and conflict management are driven by ACC and medial PFC, the results of a more pronounced Gratton effect after FAM (Colzato et al. 2015b) are in line with the idea that trial-to-trial control adjustments reflected in the Gratton effect benefited from FAM which is assumed to increase top-down control.

Hölzel et al. (2007) compared experienced and novice meditators during a concentrative meditation (akin to FAM) and found that the experienced meditators showed greater activity in the rostral ACC during meditation than the novices, even though the two groups did not differ on an arithmetic control task. Similar results were obtained in another study comparing novices and experienced meditators (Baron Short et al. 2007) by showing more activity in the ACC during FAM compared to a control task. The activity in the ACC was more consistent and sustained for experienced meditators. Related to that, Buddhist monks exhibited more activity in the ACC during FAM than during OMM (Manna et al. 2010). This suggests that the effects of meditation on the ACC and conflict monitoring do not seem to be limited to temporary state effects but carry over into daily life as a more stable "trait". Future large scale longitudinal studies should be conducted to address this issue and to disentangle short-term and long-term effects on conflict monitoring.

Improved conflict monitoring does not necessarily entail increased brain activity. Kozasa et al. (2012) compared meditators and non-meditators on a Stroop task in which semantic associations of words have to be suppressed to retrieve the color of the word. While behavioral performance was not significantly different for the two groups, compared to meditators, the non-meditators showed more activity in brain regions related to attention and motor control during incongruent trials. Given that the aim of many meditation techniques is to monitor the automatic arise of distractible sensations, such skill may become effortless by repeated meditation, therefore leading to less brain activity during the Stroop task.

Finally, a recent study Colzato et al. (2016) has shown that the congruency effect (indicating the failure to suppress task-irrelevant information) was considerably reduced after FAM than after OMM. Given that (a) FAM strengthens top-down support for relevant information and/or increases local competition between relevant and irrelevant information (Lippelt et al. 2014; Colzato et al. 2015a, b), and given that (b) congruency reflects cross talk from a currently irrelevant task or

stimulus dimension (Kiesel et al. 2010), this outcome suggests that undergoing FAM leads one to engage more in suppressing currently irrelevant information.

In sum, because FAM is assumed to increase top-down control whereas OMM is assumed to weaken top-down control, they show differential enhancing effect on conflict monitoring: compared to OMM, FAM leads to greater control strength (i.e., concentration on the goal) and a better handling of conflict management routines, see Fig. 1.

Meditate to Create

As pointed out by a recent meta-analysis there seems to be a weak but significant correlation supporting the idea that meditation enhances creativity (Lebuda et al. 2016). The authors suggested that the effect of meditation on creativity depended on the type of meditation implied. Moreover, as pointed out by Colzato et al. (2012), the weak correlation might reflect a failure to distinguish between different and dissociable processes underlying creativity, such as convergent and divergent thinking (Guilford 1950). Accordingly, Colzato et al. (2012) compared the impact of FAM and OMM on convergent thinking (a process of identifying one "correct" answer to a well-defined problem) and divergent thinking (a process aiming at generating many new ideas) in meditation practitioners. Indeed, the two types of meditation affected the two types of thinking in opposite ways: While convergent thinking tended to improve after FAM, divergent thinking was significantly enhanced after OMM. In a follow-up study Colzato et al. (2014) investigated whether this effect was modulated by prior meditation experience by comparing a group of practitioners and a group of novices. The enhancing effect of OMM on divergent thinking was found to be robust irrespective of prior experience. In contrast, while solving convergent thinking problems, practitioners used an insight strategy, as opposed to an analytical approach, significantly more often than the novices. Colzato et al. (2012) suggest that FAM and OMM induce two different, to some degree opposite cognitive control states that support state-compatible thinking styles, such as convergent and divergent thinking, respectively. In contrast to convergent thinking, divergent thinking benefits from a control state that promotes quick "jumps" from one thought to another by reducing the top-down control of cognitive processing—as achieved by OMM, see Fig. 1.

Along the same lines, Baas et al. (2014) found that specific mindfulness skills differentially predict creative performance: only the ability to observe and attend to various stimuli consistently and positively predicted creativity. Further, it has been shown that integrative body–mind training improved creativity performance on the divergent thinking task (as measured by the Torrance Tests of Creative Thinking questionnaire (Ding et al. 2014). Moreover, Ding et al. (2015) pointed out that mood and personality may be useful tools to predict individual variation in the enhancement of creative performance following meditation training.

In sum, given that OMM facilitates a control state that promotes quick "jumps" from one thought to another by reducing the top-down control of cognitive processing, see Fig. 1, it enhances divergent thinking, but not convergent thinking.

Conclusions

Meditation has the potential to enhance cognition. Although more research is needed to fully understand the effects meditation exerts on cognition, in this chapter, we pursue a mechanistically oriented, theory-driven approach that helps understand and explain the differential, dissociable effects of FAM and OMM on a wide range of cognitive (control) processes, see Fig. 1. Given that FAM increases top-down control, this type of meditation supports sustained attention and leads to a greater control strength (i.e., concentration on the goal) and a better handling of conflict management routines. On the contrary, OMM facilitates a broader distribution of attention over time and leads to a more proficient divergent thinking.

The finding of greater control strength after FAM as compared to OMM may be of particular interest because it helps to explain and understand why impulse control disorders such as attention-deficit-/hyperactivity disorder and substance abuse profit from meditation-based interventions (Cassone 2015; Witkiewitz et al. 2005). Given that most meditation programs have a one-size-fits-all design and assume that everyone benefits from the intervention more or less the same way and to more or less the same degree, we suggest that only meditation programs that are tailored to individual abilities, skills, and needs are likely to succeed.

All in all, we conclude that all meditation techniques are not equal, and that successful enhancing interventions should presuppose a theoretically guided selection of the best-suited technique.

References

Baerentsen, K. B., Hartvig, N. V., Stødkilde-Jørgensen, H., & Mammen, J. (2001). Onset of meditation explored with fMRI. *Neuroimage, 13*(6), S297.

Baijal, S., & Srinivasan, N. (2010). Theta activity and meditative states: Spectral changes during concentrative meditation. *Cognitive Processing, 11*(1), 31–38.

Brefczynski-Lewis, J. A., Lutz, A., Schaefer, H. S., Levinson, D. B., & Davidson, R. J. (2007). Neural correlates of attentional expertise in long-term meditation practitioners. *Proceedings of the National Academy of Sciences, 104*(27), 11483–11488.

Cahn, B. R., Short, E., Kose, S., Mu, Q., Borckardt, J., Newberg, A., George, M. S., et al. (2007). Regional brain activation during meditation shows time and practice effects: An exploratory fMRI study. *Evidence-Based Complementary and Alternative Medicine, 7*(1), 121–127.

Baas, M., Nevicka, B., & Ten Velden, F. S. (2014). Specific mindfulness skills differentially predict creative performance. *Personality and Social Psychology Bulletin, 40*(9), 1092–1106.

Botvinick, M. (2007). Conflict monitoring and decision making: Reconciling two perspectives on anterior cingulate function. *Cognitive, Affective and Behavioral Neuroscience, 7*, 356–366.

Botvinick, M., Nystrom, L. E., Fissell, K., Carter, C. S., & Cohen, J. D. (1999). Conflict monitoring versus selection-for-action in anterior cingulate cortex. *Nature, 402*(6758), 179–181.

Botvinick, M. M., Braver, T. S., Barch, D. M., Carter, C. S., & Cohen, J. D. (2001). Conflict monitoring and cognitive control. *Psychological Review, 108*, 624–652.

Botvinick, M. M., Cohen, J. D., & Carter, C. S. (2004). Conflict monitoring and anterior cingulate cortex: An update. *Trends in Cognitive Sciences, 8*(12), 539–546.

Brefczynski-Lewis, J. A., Lutz, A., Schaefer, H. S., Levinson, D. B., & Davidson, R. J. (2007). Neural correlates of attentional expertise in long-term meditation practitioners. *Proceedings of the National Academy of Sciences, 104*(27), 11483–11488.

Cahn, B. R., Delorme, A., & Polich, J. (2010). Occipital gamma activation during Vipassana meditation. *Cognitive Processing, 11*(1), 39–56.

Cahn, B. R., & Polich, J. (2006). Meditation states and traits: EEG, ERP, and neuroimaging studies. *Psychological bulletin*, *132*(2), 180–211.

Carter, O. L., Presti, D. E., Callistemon, C., Ungerer, Y., Liu, G. B., & Pettigrew, J. D. (2005). Meditation alters perceptual rivalry in Tibetan Buddhist monks. *Current Biology, 15*(11), R412–R413.

Cassone, A. R. (2015). Mindfulness training as an adjunct to evidence-based treatment [illegible] within families. *Journal of Attention Disorders*, *19*, 147–157.

Chan, D., & Woollacott, M. (2007). Effects of level of meditation experience on attentional focus: Is the efficiency of executive or orientation networks improved? *The Journal of Alternative and Complementary Medicine*, *13*, 651–658.

Chiesa A., & Seretti, A., (2009). Mindfulness-based stress reduction for stress management in healthy people: A review and meta-analysis. *The Journal of Alternative and Complementary Medicine*, *15*, 593–600.

Crescentini, C., Capurso, V., Furlan, S., & Fabbro, F. (2016a). Mindfulness-Oriented meditation for primary school children: Effects on attention and psychological well-being. *Frontiers in Psychology*, *7*, 805.

Crescentini, C., Chittaro, L., Capurso, V., Sioni, R., & Fabbro, F. (2016b). Psychological and physiological responses to stressful situations in immersive virtual reality: Differences between users who practice mindfulness meditation and controls. *Computers in Human Behavior*, *59*, 304–316.

Crescentini, C., & Capurso, V. (2015). Mindfulness meditation and explicit and implicit indicators of personality and self-concept changes. *Frontiers in Psychology*, *6*, 44.

Colzato, L. S., Ozturk, A., & Hommel, B. (2012). Meditate to create: The impact of focused-attention and open-monitoring training on convergent and divergent thinking. *Frontiers in Psychology, 3*(116), 1–5.

Colzato, L. S., Sellaro, R., Samara, I., Baas, M., & Hommel, B. (2015a). Meditation-induced states predict attentional control over time. *Consciousness and Cognition, 37*, 57–62.

Colzato, L. S., Sellaro, R., Samara, I., & Hommel, B. (2015b). Meditation-induced cognitive-control states regulate response-conflict adaptation: Evidence from trial-to-trial adjustments in the Simon task. *Consciousness and Cognition, 35*, 110–114.

Colzato, L. S., van der Wel, P., Sellaro, R., & Hommel, B. (2016). A single bout of meditation biases cognitive control but not attentional focusing: Evidence from the global-local task. *Consciousness and Cognition, 39*, 1–7.

Colzato, L. S., Szapora, A., Lippelt, D., & Hommel, B. (2017). Prior meditation practice modulates performance and strategy use in convergent- and divergent-thinking problems. *Mindfulness, 8*, 10–18

D'Esposito, M. (2007). From cognitive to neural models of working memory. *Philosophical Transactions of the Royal Society B: Biological Sciences*, *362*, 761–772.

Delgado-Pastor, L. C., Perakakis, P., Subramanya, P., Telles, S., & Vila, J. (2013). Mindfulness (Vipassana) meditation: Effects on P3b event-related potential and heart rate variability. *International Journal of Psychophysiology, 90*(2), 207–214.

Ding, X., Tang, Y. Y., Tang, R., & Posner, M. I. (2014). Improving creativity performance by short-term meditation. *Behavioral and Brain Functions, 10*(9), 1–8.

Ding, X., Tang, Y. Y., Deng, Y., Tang, R., & Posner, M. I. (2015). Mood and personality predict improvement in creativity due to meditation training. *Learning and Individual Differences*, *37*, 217–221.

Duncan, J. (2001). An adaptive coding model of neural function in prefrontal cortex. *Nature Reviews Neuroscience*, *2*, 820–829.

Eriksen, B. A., & Eriksen, C. W. (1974). Effects of noise letters upon the identification of a target letter in a nonsearch task. *Perception & Psychophysics*, *16*, 143–149.

Fan, J., McCandliss, B. D., Sommer, T., Raz, A., & Posner, M. I. (2002). Testing the efficiency and independence of attentional networks. *Journal of Cognitive Neuroscience, 14*(3), 340–347.

Farb, N. A., Segal, Z. V., & Anderson, A. K. (2013). Mindfulness meditation training alters cortical representations of interoceptive attention. *Social Cognitive and Affective Neuroscience, 8,* 15–26.

Guilford, J. P. (1950). Creativity. *American Psychologist, 5,* 444–454.

Hasenkamp, W., & Barsalou, L. W. (2012). Effects of meditation experience on functional connectivity of distributed brain networks. *Frontiers in Human Neuroscience, 6*(38), 1–14.

Hasenkamp, W., Wilson-Mendenhall, C. D., Duncan, E., & Barsalou, L. W. (2012). Mind wandering and attention during focused meditation: A fine-grained temporal analysis of fluctuating cognitive states. *Neuroimage, 59*(1), 750–760.

Hodgins, H. S., & Adair, K. C. (2010). Attentional processes and meditation. *Consciousness and Cognition, 19*(4), 872–878.

Hölzel, B. K., Ott, U., Hempel, H., Hackl, A., Wolf, K., Stark, R., et al. (2007). Differential engagement of anterior cingulate and adjacent medial frontal cortex in adept meditators and non-meditators. *Neuroscience Letters, 421*(1), 16–21.

Hommel, B. (2015). Between persistence and flexibility: The Yin and Yang of action control. In A. J. Elliot (Ed.), *Advances in Motivation Science*, (Vol. 2, pp. 33–67). New York: Elsevier.

Kiesel, A., Steinhauser, M., Wendt, M., Falkenstein, M., Jost, K., Philipp, A., et al. (2010). Control and interference in task switching—A review. *Psychological Bulletin*, *136*, 849–874.

Kozasa, E. H., Sato, J. R., Lacerda, S. S., Barreiros, M. A., Radvany, J., Russel, T. A., et al. (2012). Meditation training increases brain efficiency in an attention task. *Neuroimage, 59*(1), 745–749.

Lazar, S. W., Bush, G., Gollub, R. L., Fricchione, G. L., Khalsa, G., & Benson, H. (2000). Functional brain mapping of the relaxation response and meditation. *Neuroreport, 11*(7), 1581–1585.

Lebuda, I., Zabelina, D. L., & Karwowski, M. (2016). Mind full of ideas: A meta-analysis of the mindfulness–creativity link. *Personality and Individual Differences, 93*, 22–26.

Lippelt, D. P., Hommel, B., & Colzato, L. S. (2014). Focused attention, open monitoring and loving kindness meditation: Effects on attention, conflict monitoring and creativity. *Frontiers in Psychology*, *5*, 1083.

Lutz, A., Slagter, H. A., Dunne, J. D., & Davidson, R. J. (2008). Attention regulation and monitoring in meditation. *Trends in Cognitive Sciences, 12*(4), 163–169.

Manna, A., Raffone, A., Perrucci, M. G., Nardo, D., Ferretti, A., Tartaro, A., et al. (2010). Neural correlates of focused attention and cognitive monitoring in meditation. *Brain Research Bulletin, 82*(1–2), 46–56.

Murphy, M., Donavon, S. (1997). *The physical and psychological effects of meditation: A review of contemporary research with a comprehensive bibliography 1931–1996*. Sausalito, CA: Institute of Noetic Sciences.

Slagter, H. A., Lutz, A., Greischar, L. L., Francis, A. D., Nieuwenhuis, S., Davis, J., et al. (2007). Mental training affects distribution of limited brain resources. *PLoS Biology, 5*(6), e138.

Tang, Y. Y., Ma, Y., Wang, J., Fan, Y., Feng, S., Lu, Q., et al. (2007). Short-term meditation training improves attention and self-regulation. *Proceedings of the National Academy of Sciences, 104*(43), 17152–17156.

Tang, Y. Y., Ma, Y., Fan, Y., Feng, H., Wang, J., Feng, S., et al. (2009). Central and autonomic nervous system interaction is altered by short-term meditation. *Proceedings of the National Academy of Sciences, 106*(22), 8865–8870.

Tang, Y. Y., Qilin, L., Gen, X., Stein, E. A., Yang, Y., & Posner, M. I. (2010). Short-term meditation induces white matter changes in the anterior cingulate. *Proceedings of the National Academy of Sciences, 107*(35), 15649–15652.

Tang, Y., Tang, R., Lu, Q., Feng, H., & Posner, M. (2015). Short-term meditation increases blood flow in anterior cingulate cortex and insula. *Frontiers in Psychology, 6*, 212.

Tops, M., Boksem, M. A., Quirin, M., IJzerman, H., & Koole, S. L. (2014). Internally-directed cognition and mindfulness: An integrative perspective derived from reactive versus predictive control systems theory. *Frontiers in Psychology, 5*(429), 1–47.

Travis, F., & Shear, J. (2010). Focused attention, open monitoring and automatic self-transcending: Categories to organize meditations from Vedic, Buddhist and Chinese traditions. *Consciousness and Cognition, 19*(4), 1110–1118.

Tsai, J. F., Jou, S. H., Cho, W., & Lin, C. M. (2013). Electroencephalography when meditation advances: A case-based time-series analysis. *Cognitive Processing, 14*(4), 371–376.

Tomasino, B., Fregona, S., Skrap, M., & Fabbro, F. (2013). Meditation-related activations are modulated by the practices needed to obtain it and by the expertise: An ALE meta-analysis study. *Frontiers in Human Neuroscience*, *6*, 346.

Vago, D. R., & Silbersweig, D. A. (2012). Self-awareness, self-regulation, and self-transcendence (S-ART): A framework for understanding the neurobiological mechanisms of mindfulness. *Frontiers in Human Neuroscience, 6*(296), 1–30.

Valentine, E. R., & Sweet, P. L. (1999). Meditation and attention: A comparison of the effects of concentrative and mindfulness meditation on sustained attention. *Mental Health, Religion and Culture, 2*(1), 59–70.

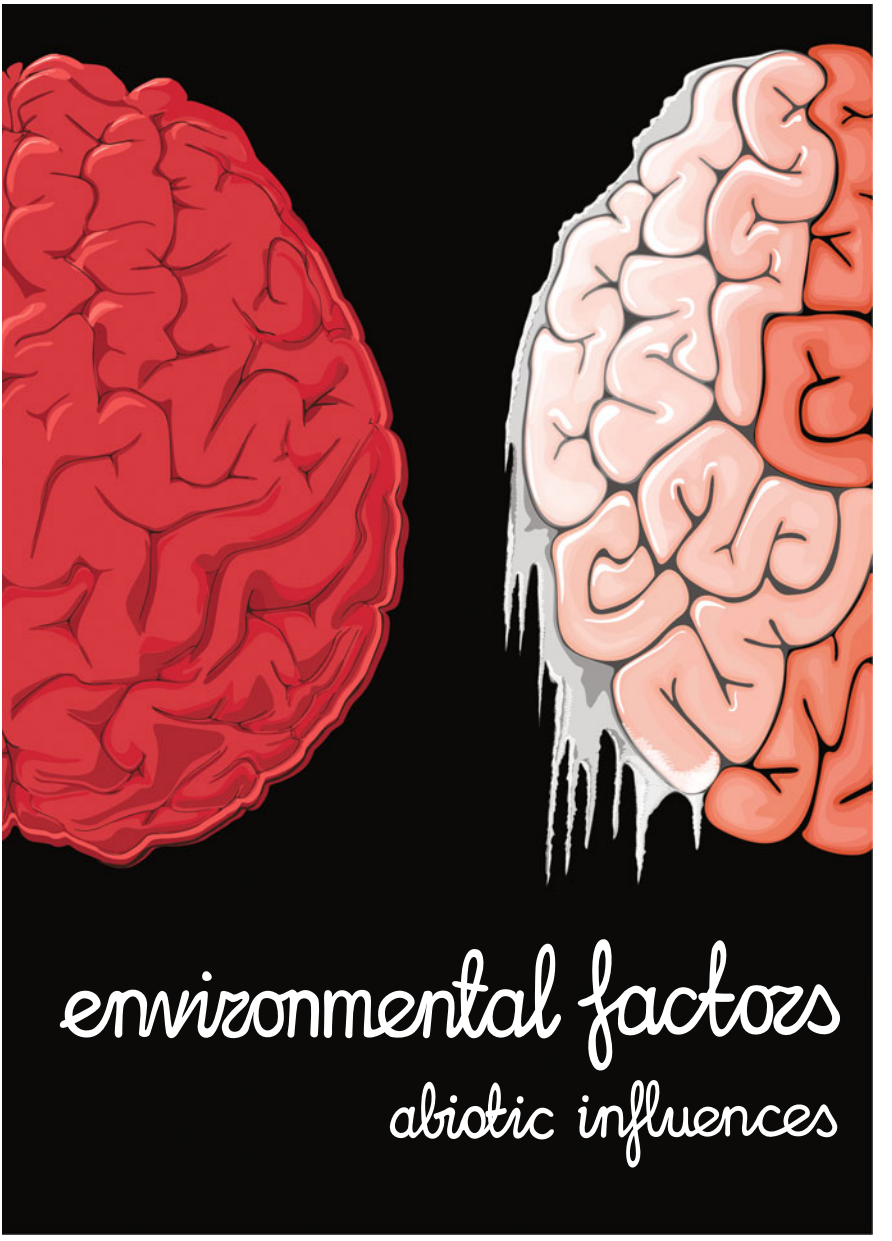
van Leeuwen, S., Müller, N. G., & Melloni, L. (2009). Age effects on attentional blink performance in meditation. *Consciousness and Cognition*, *18*(3), 593–599.

van Vugt, M. K., & Slagter, H. A. (2014). Control over experience? Magnitude of the attentional blink depends on meditative state. *Consciousness and Cognition*, *23*, 32–39.

Wachholtz, A. B., & Pargament, K. I. (2005). Is spirituality a critical ingredient of meditation? Comparing the effects of spiritual meditation, secular meditation, and relaxation on spiritual, psychological, cardiac, and pain outcomes. *Journal of behavioral medicine*, *28*(4), 369–384.

Witkiewitz, K., Marlatt, G. A., Walker, D. (2005). Mindfulness-based relapse prevention for alcohol and substance use disorders. *Journal Cognitive Psychotherapy, 19*, 211–228.

Xue, S., Tang, Y. Y., & Posner, M. I. (2011). Short-term meditation increases network efficiency of the anterior cingulate cortex. *Cognitive Neuroscience and Neuropsychology, 22*(12), 570–574.


environmental factors
abiotic influences

Part VI
Environmental Factors—Abiotic Influences

Introduction

The present part aims to explore how to enhance cognitive processes via environmental abiotic factors: identifiable "nonliving" elements in the physical world that affect our mood and mental states. The most prominent of these factors are aromas and temperature.

Similarly to the food supplements industry, also the aromas trades industry is booming with estimated sales in millions of US dollars. According to a recent study in the UK (Posadzki et al. 2013), aromatherapy, the therapeutic use of essential oils from plants, is the third most popular complementary and alternative medicine after herbal medicine and homeopathy. Chapter "Aromas" will scientifically evaluate the popular belief that aromas may help to improve our mood and cognition. Even if scientific evidence is still scarce, it will described how (i.e., putative effect on the sympathetic and parasympathetic nervous system) and under which circumstances aromas can be considered a valuable cognitive enhancer.

Besides aromas, another crucial environmental factor is temperature whose enhancing effect on social cognition seems to be embodied (see Chapter "Temperature"). Given the climate changes due to global warming, the effect of temperature on the way we perceive and interpret the world is expected to gain more interest in the next decades. Indeed, one of the stable changes of climate is the gradual increment of temperature which, besides the melting of ice caps, might affect cooperation and interpersonal functioning (IJzerman and Semin 2009, 2010).

References

IJzerman, H., & Semin, G. R. (2009). The thermometer of social relations mapping social proximity on temperature. *Psychological Science, 20*(10), 1214–1220.

IJzerman, H., & Semin, G. R. (2010). Temperature perceptions as a ground for social proximity. *Journal of Experimental Social Psychology, 46*(6), 867–873.

Posadzki, P., Watson, L. K., Alotaibi, A., & Ernst, E. (2013). Prevalence of use of complementary and alternative medicine (CAM) by patients/consumers in the UK: Systematic Review of Surveys. *Clinical Medicine, 13*(2), 126–131.


aromas

Aromas

Roberta Sellaro and Lorenza S. Colzato

Introduction

The interest in how aromas shape our daily life is constantly growing. Notably, according to a recent study in the UK (Posadzki et al. 2013), aromatherapy, the therapeutic use of essential oils from plants, is the third most popular complementary and alternative medicine after herbal medicine and homeopathy. That is, many people in western societies rely on the use of aromas with the purpose of altering one's mood, as well as cognitive, psychological or physical well-being. Even though the popular believe supports the idea that aromas may help to improve general well-being, the scientific evidence is still scarce. According to a recent meta-analysis, there seem to be some indications, even if the evidence is not conclusive, that aromas might have beneficial effects on health care and stress management (Hur et al. 2014). However, the limitations of many of studies included in the meta-analysis are that they did not employ blinding of patients, practitioners, and assessors (Hur et al. 2014). Nevertheless, it might be that aromatherapy exerts its effect on reducing stress by decreasing sympathetic nervous system activity and, at the same time, by activating the parasympathetic nervous system (Duan et al. 2007). In recent years, it has been demonstrated that aromas have beneficial effects not only in clinical settings, but also exhibit significant enhancing effects on how people perceive and process the world around them and alter the way they regulate attention and emotion.

R. Sellaro (✉) · L.S. Colzato
Cognitive Psychology Unit and Leiden Institute for Brain and Cognition, Leiden University, Wassenaarseweg 52, 2333 AK Leiden, The Netherlands
e-mail: r.sellaro@fsw.leidenuniv.nl

L.S. Colzato
Institute of Cognitive Neuroscience, Faculty of Psychology, Ruhr University Bochum, Bochum, Germany

L.S. Colzato, *Theory-Driven Approaches to Cognitive Enhancement*,
DOI 10.1007/978-3-319-57505-6_17

This chapter will focus on the evidence that distinctive aromas exert beneficial effects on cognition. First, we will describe the physiological effects that are associated with aroma exposure. Second, we will outline the available studies investigating the effect of arousing (e.g., peppermint) and calming (e.g., lavender) olfactory fragrances. The studies indicate that arousing olfactory fragrances have the potential to enhance cognitive functioning, whereas calming olfactory fragrances have the potential to promote prosocial and consumer behavior. Finally, we will discuss some critical considerations on the methodological limits of the research conducted so far and proposals for future studies before proceeding to the general conclusions.

Physiological Effects Associated with Aroma Exposure

The literature suggests that different aromas cause specific physiological alterations in the nervous system that can exert a direct effect on cognition, though the cognitive effects are also likely to be mediated and/or magnified by changes in mood, expectancy, and previously formed contextual association with a given odor (Johnson 2011; Herz 2009; Hongratanaworakit 2004; Jellinek 1997). For instance, animal studies have shown that aroma-specific compounds can enter the bloodstream via the nasal mucosa and, consequently, alter neural activity (Jirovetz et al. 1990), possibly because of the close proximity between olfactory and limbic systems (Johnson 2011; Diego et al. 1998).

The documented physiological effects of aromas on the nervous system are mainly characterized by changes in the levels of both autonomic (e.g., heart rate, skin conductance) and cortical (e.g., brain wave activity) arousal, with some aromas increasing such levels while others decrease them (Jellinek 1997). Importantly, increases in autonomic and cortical arousal levels are assumed to have a stimulating effect, while a reduction of these levels is reckoned to have a sedative/relaxing effect (Stern et al. 2001).

Physiological parameters that have been used as indexes for evaluating the stimulating versus sedative properties of aromas include heart rate, electrodermal activity, brain waves, pupil dilation/constriction or eye blink rate.

Physiological stimulating properties have been documented for aromas such as lemon, jasmin, patchouli, peppermint, sweet orange, and rosemary. For instance, an increase in heart rate has been observed following exposure to lemon (Kikuchi et al. 1991) and sweet orange aroma (Hongratanaworakit and Buchbauer 2003), while peppermint has been found to increase skin conductance during a vigilance task (Parasuraman et al. 1992). Increases in beta wave activity and, hence, higher levels of arousal, have been observed upon presentation of jasmin odor (Sugano 1991, 1989), which has also been found to increase the contingent negative variation (CNV), an event-related potential component that can be taken to reflect the degree of arousal (Janssen et al. 1978; Ashton et al. 1974). An increase in the CNV has also been reported when exposing participants to patchouli and peppermint (Manley

1993). Finally, rosemary exposure has been shown to cause pupil dilation, which likely reflects an increase of arousal (Steiner et al. 1977). Consistent with the aforementioned physiological effects, research has shown that peppermint—probably one of the most studied arousing aromas—improves athletic task performance (Meamarbashi 2014; Meamarbashi and Rajabi 2013; Raudenbush et al. 2001), typing performance (Barker et al. 2003), subjective alertness and vigilance (Moss et al. 2008; Norrish and Dwyer 2005; Warm et al. 1991), increases alertness while reducing frustration after driving for prolonged periods (Raudenbush et al. 2009), reduces perceived workload and effort and increase self-evaluated physical performance and energy in athletes (Raudenbush et al. 2002), alters electrophysiological activity during sleep (Badia et al. 1990), and acts as an excellent analgesic (Rhind 2012). These findings are consistent with the assumption that aromas may have pharmacological properties. In particular with regard to peppermint, it has been proposed that one of its main components, i.e., menthol, can supply the brain with more oxygen, which is likely to improve thinking, alertness, and enhance learning capacity by stimulating and refreshing the mind (Meamarbashi and Rajabi 2013).

Physiological relaxing/sedative effects have been reported following exposure to aromas such as alpha-pinene, bergamot, chamomile, cineol, lavender, rose, sandalwood, spiced apple, and ylang-ylang. For instance, rose aroma has been found to decrease heart rate (Kikuchi et al. 1991), and 2-Phenylethanol—a fragrance similar to the odor of roses—has been shown to decrease skin conductance levels (Brauchli et al. 1995). Similarly, ylang–ylang aroma has been found to induce significant decreases in blood pressure and heart rate (Hongratanaworakit and Buchbauer 2004). Increased alpha activity, which is associated with a mentally relaxed state, has been observed after exposure to spiced apple (Lorig and Schwartz 1988), lavender, cineol, sandalwood, alpha-pinene (Diego et al. 1998; Sugano 1989), and ylang–ylang (Ishigjchi et al. 2008), which was also found to reduce the amplitude of the auditory P300, thereby reflecting a calming effect (Watanabe et al. 2013; Iino et al. 2011). Moreover, exposure to lavender (Torii et al. 1988), bergamot, chamomile, and sandalwood (Manley 1993) has been found to cause a decrease of the CNV magnitude, mirroring the reduction that is observed after taking a nap (Torii et al. 1988). Finally, sandalwood oil has been found to reduce eye blink rate (Hongratanaworakit et al. 2004). Consistently, research has found that lavender—one of the most recommended aromas to induce relaxation (La Torre 2003)—has stress relieving, relaxing, calming, and sedative properties (Rhind 2012). Indeed, it reduces state anxiety (Bradley et al. 2009; Diego et al. 1998), fatigue (Sakamoto et al. 2005), salivary chromogranin A (a marker of stress) when exposing participants to a stress-inducing arithmetic task (Toda and Morimoto 2008), and self-related measures of anxiety and worry in patients suffering from generalized anxiety disorder, similarly to antianxiety drugs (Woelk and Schläfke 2010). Furthermore, lavender has been found to be an excellent natural remedy to treat insomnia and improve sleep quality (Hirokawa et al. 2012; Chien et al. 2012; Moeini et al. 2011), and to be useful in the treatment of both acute and chronic pain (Ching 1999). These findings fit with the proposal that lavender can act

pharmacologically by modulating activity of cyclic adenosine monophosphate, whose reduction is associated with sedation (Lis-Balchin and Hart 1999). The proposal that lavender induces sedation via neuropharmacological mechanisms is also supported by the observation that linalool, a principal component of lavender, inhibits glutamate binding, with resulting sedative effects (Elisabetsky et al. 1995).

In sum, the aforementioned evidence shows that aromas can produce relevant physiological changes and possibly have pharmacological properties, and that, despite some inconsistencies across studies (see, e.g., Herz 2009), such changes are mostly aroma-specific. More interestingly, as we will show in the next paragraph, aroma-specific physiological changes often produce corresponding aroma-specific effects on cognitive and social functioning, and consumer behavior (Roxanaa and Ioan 2013; Johnson 2011; Herz 2009). In particular, in reviewing the relevant literature, we will show that while stimulating aromas seem to be effective in enhancing cognitive functioning, relaxing aromas are more effective in enhancing social functioning and in modulating consumer behavior. To account for this dissociation we have recently proposed that, by virtue of their stimulating versus relaxing properties, aromas can affect cognitive control states by biasing an individual's attention toward either local or global representational levels, respectively (Sellaro et al. 2015a, b; Colzato et al. 2014). Importantly, drawing attention toward local representational levels is likely to induce a more focused/exclusive attentional state, which is expected to be beneficial for concentration and cognitive functioning. Conversely, drawing attention toward global representational levels is likely to induce a broader/integrative attentional state, which may have a negative impact on concentration and cognitive functioning. However, and more interestingly, given that a more integrative control state is known to boost self-other overlap (Hommel et al. 2009) and to favor approach over avoidance behavior (Donovan and Rossiter 1982; Mehrabian and Russel 1974), the exposure to calming scents is expected to have positive effects as well, namely, to promote social functioning and consumer behavior. The literature, as reviewed in the next paragraph, seems to support our proposal.

Differential Effects of Aromas on Cognitive and Social Functioning, and Consumer Behavior

Under this section we will describe relevant findings documenting that aroma exposure, besides affecting physiology (Johnson 2011; Herz 2009), mood (Johnson 2011; Herz 2009; Moss et al. 2008; Diego et al. 1998), athletic performance (e.g., Meamarbashi 2014; Meamarbashi and Rajabi 2013; Raudenbush et al. 2001), alertness, vigilance and fatigue (e.g., Raudenbush et al. 2009; Moss et al. 2008; Norrish and Dwyer 2005; Sakamoto et al. 2005; Barker et al. 2003; Raudenbush et al. 2002; Warm et al. 1991), anxiety (e.g., Woelk and Schläfke 2010; Bradley et al. 2009; Diego et al. 1998), stress response (e.g., Toda and Morimoto 2008), sleep quality (e.g., Hirokawa et al. 2012; Chien et al. 2012; Moeini et al. 2011),

and pain perception (e.g., Villemure et al. 2003; Ching 1999), can also modulate memory functioning (Moss et al. 2008, 2003), dual-task performance (Ho and Spence 2005), the allocation of attention in time (Colzato et al. 2014; Moss et al. 2003, 2008), social functioning (Sellaro et al. 2015a, b; Grimes 1999), and consumer behavior (Morrison et al. 2011; Guéguen and Petr 2006).

In a series of studies, Moss et al. (2003, 2008) assessed the effects of different types of aromas on several facets of memory performance by administering participants, during aroma exposure, a battery of tests to evaluate speed of memory, quality of memory, working memory, and long-term memory. In the first of these studies, the effects of rosemary, lavender, and no odor (control) were compared across groups (Moss et al. 2003). It was found that, compared to lavender and to the control condition, exposure to the stimulating fragrance of rosemary significantly improved long-term memory. In contrast, lavender was found to have a detrimental effect on working memory and overall quality of memory. Similar results were observed in a follow-up study (Moss et al. 2008) comparing the effects of peppermint and ylang-ylang with a no-aroma condition: compared to the relaxing aroma of ylang-ylang, peppermint improved overall quality of memory, working memory and long-term memory.

Ho and Spence (2005) provided evidence suggesting that peppermint can increase concentration levels under conditions of high-task demands. They employed a dual-task paradigm requiring participants to perform a Rapid Serial Visual Presentation (RSVP) task (i.e., to detect a target digit embedded in a sequence of distracter digits) and a vibrotactile discrimination task (i.e., to discriminate the location of vibrotactile stimuli presented on the front or back of their torso). For the latter task, responses could be either congruent or incongruent with the tactile stimulation (easy vs. difficult condition). During the execution of the dual-task, participants were exposed to either peppermint aroma or clean air (control). Improved performance was observed during peppermint exposure, but only for the difficult condition of vibrotactile discrimination task. Based on these findings, the authors proposed that peppermint can promote cognitive control processes that inhibit incorrect responses under conditions of high-task difficulty.

The hypothesis that arousing and calming olfactory fragrances can differentially affect the individual's attention, by biasing it toward either local or global representational levels, respectively, was tested directly in a recent study by Colzato et al. (2014). In this study, participants performed an "attentional blink" (AB) task (Raymond et al. 1992), known to produce a deficit in reporting the second of two target stimuli presented in close succession in a rapid sequence of distractors (i.e., AB effect), while being exposed to peppermint, lavender, or no aroma. Importantly, this deficit is known to result from the fact that once attentional resources are allocated to the processing of the first target, they become temporarily unavailable for the processing of the second one (Dux and Marois 2009). Therefore, attentional overinvestment, in this case, is likely to be counterproductive. Consistently, in two experiments, using a between-subjects and a within-subjects design, respectively, it was found that while peppermint produced a larger AB effect, whereas lavender tended to decrease it.

An interesting line of research has focused on the potential effects of aromas to promote social functioning. For instance, Grimes (1999) showed that exposure to relaxing odors such as vanilla and lavender, as compared to no odor, might promote helping behavior. She found that, after exposure to these odors, students reported to be more willing to spend time on voluntary work. This result fits with the idea that relaxing aromas can increase self-other overlap. Direct evidence supporting this possibility was recently provided by Sellaro at el. (2015a). In this study, pairs of participants were exposed to peppermint, lavender, or no-aroma (control) during the execution of a joint Simon task (Hommel et al. 2009; Sebanz et al. 2003), a turn-taking paradigm requiring the participant and a confederate to perform complementary parts of the same task. Importantly, this task is known to provide a well-reliable measure of the degree of self-other integration: a more pronounced joint Simon effect is indicative of higher self-other overlap (Colzato et al. 2012a, b, 2013). Compared to the control condition, it was found that while peppermint produced a more pronounced joint Simon effect (i.e., it reduced self-other overlap), lavender produced a less pronounced effect (i.e., it increased self-other overlap). Therefore, these results strongly support the hypothesis that arousing versus calming aromas can differentially bias an individual's control state toward either a more exclusive or a more inclusive processing mode, respectively. Consistently, in another study (Sellaro et al. 2015b), it was found that interpersonal trust—which is likely to depend on the degree of self-other overlap (Hommel and Colzato 2015)—significantly increased in the presence of lavender, as compared to peppermint and no aroma.

Finally, a set of studies provided evidence that aroma exposure can also affect consumer behavior by possibly promoting approach behavior (i.e., the desire to stay, explore, and affiliate). For instance, research has shown that people tend to stay longer in a commercial area (Knasco 1989) and to have a positive perception of mall environment and product quality (Chebat and Michon 2003) when exposed to pleasant fragrances. Guéguen and Petr (2006) showed that the positive effects of aromas on consumer behavior can be aroma-specific. They conducted an experiment in a restaurant, in which they monitored the customers' length of stay and the amount of purchasing under three different occasions, namely, in the presence of lavender (i.e., relaxing aroma), lemon (i.e., stimulating aroma), or no aroma (control condition). They found that, compared to the control condition, lavender, but not lemon, increased the amount of time customers spent in the restaurant and the amount of purchasing. In a similar vein, more recently, Morrison et al. (2011) showed that vanilla aroma has a positive effect on customers' amount of time and money spent in a store and their satisfaction with the shopping experience.

All in all, the results of the available studies provide evidence favoring the idea that aromas may be a useful tool to promote cognitive enhancement, social and consumer behavior. Furthermore, the aforementioned findings suggest that aroma-induced effects can depend on the specific arousing versus calming properties of a given aroma. Specifically, these findings seem to suggest that while cognitive functioning is more likely to benefit from the exposure to arousing fragrances, social and consumer behavior are more likely to benefit from the exposure

to calming fragrances. However, as we will highlight in the following section, some limitations inherent in aroma studies call for further research to confirm these claims. Moreover, we acknowledge that research on the effects of aroma on cognitive and social functioning is still limited, thus preventing firm conclusions to be drawn.

Critical Considerations

As argued elsewhere (Johnson 2011; Herz 2009), the research field focusing on the effects of aromas on physiology, mood, cognition, and social/consumer behavior suffers from some important shortcomings, which may explain possible inconsistency across studies. Probably the most important one concerns the fact that the majority of these studies did not include physiological measures to assess aroma reactivity in terms of autonomic and cortical arousal, but relied only on self-report measures. Without more objective measures, the hypothesis that aroma-specific effects are caused by virtue of their arousing versus calming properties remains speculative, especially because other factors, such as subjective hedonic evaluations and expectancies, can play a crucial role, by either inverting or magnifying the expected effects. For instance, Campenni et al. (2004) provided evidence showing that the simple suggestion that a given odor would be relaxing (vs. arousing) is sufficient to decrease (vs. increase) HR and skin conductance, regardless of the presented odor and even when no odor is presented. Therefore, this research field would undoubtedly benefit from the collection of both physiological and cognitive measures, and from the assessment of their possible association.

However, the inclusion of objective measures of arousal levels alone cannot be sufficient to rule out the possible influence of several other factors, unless an extensive examination of their possible role is performed, which is usually missing. Aroma effectiveness is likely to depend on the interplay between aroma properties, personality characteristics, and experimental procedures. For instance, odor perception is known to be influenced by previously formed contextual associations with a given odor (Ayabe-Kanamura et al. 1998; Moncrieff 1966), meaning that culture may play a crucial role, as it may determine the framework upon which these associations are formed. This means that the same aroma can have different effects across cultures. Therefore, more research is needed to assess possible cultural differences in reaction to specific aromas. Personal experiences and resulting individual differences in the subjective evaluation of specific aromas may represent important confounding factors as well, as they can cause unexpected effects to be found and prevent generalization across different studies and labs (Goel and Lao 2006; Villemeure et al. 2003). Also, individual differences in terms of olfactory sensitivity need to be considered, as this may cause some individuals to be more or less sensitive to specific aromas. This implies that it is crucial to adopt standardized tests to assess participants' olfactory sensitivity along with the inclusion of self-report ratings of the scents. Another aspect that needs to be considered pertains

the possible role of sex differences. Women are usually more sensitive than men to aromas, especially when tested during the menstrual cycle (Doty et al. 1981), and they seem to be more emotionally reactive to aromas (Chen and Dalton 2005). This suggests that women can benefit more than men from aroma exposure, meaning that in evaluating aroma-induced effects and in the attempt to generalize them, it is important to take into consideration the possible role of sex differences.

Other crucial considerations concern methodological aspects. For instance, one problem pertains to the nature (natural vs. synthetic) of the used aroma. It is said that natural aromas are superior to the synthetic ones, but no studies have directly compared natural and synthetic versions of the same aroma to verify this claim. Importantly, the available studies vary widely with respect to whether synthetic or natural aromas were used, and often they do not even specify that. However, to the extent to which this claim is true, inconsistencies across studies are likely to arise. Therefore, research aimed at comparing the effects of synthetic or natural aromas is highly recommended. Moreover, differences in terms of duration and mode (continuous vs. periodic) of aroma exposure, doses, and the presence (vs. absence) of a placebo condition and of a control (aroma) condition, make it impossible to compare the results across different studies. Therefore, more consistent methodological practice is needed.

Taken together, the above-mentioned considerations suggest the necessity of conducting additional extensive research before concluding that aromas can affect and enhance cognitive and social functioning.

Conclusion

In sum, the present review suggests that aroma may represent a highly valuable cognitive enhancement tool. However, it also suggests that more effort is needed to enhance the methodological quality of research and to shed light on how and under what circumstances aromas can affect behavior.

References

Ashton, H., Millman, J. E., Telford, R., & Thompson, J. W. (1974). The effect of caffeine, nitrazepam and cigarette smoking on the contingent negative variation in man. *Electroencephalography and Clinical Neurophysiology, 37*(1), 59–71.

Ayabe-Kanamura, S., Schicker, I., Laska, M., Hudson, R., Distel, H., Kobayakawa, T., et al. (1998). Differences in perception of everyday odors: A Japanese-German cross-cultural study. *Chemical Senses, 23*(1), 31–38.

Badia, P., Wesensten, N., Lammers, W., Culpepper, J., & Harsh, J. (1990). Responsiveness to olfactory stimuli presented in sleep. *Physiology & Behavior, 48*(1), 87–90.

Barker, S., Grayhem, P., Koon, J., Perkins, J., Whalen, A., & Raudenbush, B. (2003). Improved performance on clerical tasks associated with administration of peppermint odor. *Perceptual and Motor Skills, 97*(3), 1007–1010.

Bradley, B. F., Brown, S. L., Chu, S., & Lea, R. W. (2009). Effects of orally administered lavender essential oil on responses to anxiety-provoking film clips. *Human Psychopharmacology: Clinical and Experimental, 24*(4), 319–330.

Brauchli, P., Rüegg, P. B., Etzweiler, F., & Zeier, H. (1995). Electrocortical and autonomic alteration by administration of a pleasant and an unpleasant odor. *Chemical Senses, 20*(5), 505–515.

Campenni, C. E., Crawley, E. J., & Meier, M. E. (2004). Role of suggestion in odor-induced mood change. *Psychological Reports, 94*(3 Suppl), 1127–1136.

Chebat, J. C., & Michon, R. (2003). Impact of ambient odors on mall shoppers' emotions, cognition, and spending: A test of competitive causal theories. *Journal of Business Research, 56*(7), 529–539.

Chen, D., & Dalton, P. (2005). The effect of emotion and personality on olfactory perception. *Chemical Senses, 30*(4), 345–351.

Chien, L. W., Cheng, S. L., & Liu, C. F. (2012). The effect of lavender aromatherapy on autonomic nervous system in midlife women with insomnia. *Evidence-Based Complementary and Alternative Medicine, 2012*, 740813–740813.

Ching, M. (1999). Contemporary therapy: Aromatherapy in the management of acute pain? *Contemporary Nurse, 8*(4), 146–151.

Colzato, L. S., de Bruijn, E. R., & Hommel, B. (2012a). Up to "Me" or Up to "Us"? The impact of self-construal priming on cognitive self-other integration. *Frontiers in Psychology, 3,* 341.

Colzato, L. S., Zech, H., Hommel, B., Verdonschot, R., van den Wildenberg, W. P., & Hsieh, S. (2012b). Loving-kindness brings loving-kindness: The impact of Buddhism on cognitive self–other integration. *Psychonomic Bulletin & Review, 19*(3), 541–545.

Colzato, L. S., van den Wildenberg, W. P., & Hommel, B. (2013). Increasing self–other integration through divergent thinking. *Psychonomic Bulletin & Review, 20*(5), 1011–1016.

Colzato, L. S., Sellaro, R., Paccani, C. R., & Hommel, B. (2014). Attentional control in the attentional blink is modulated by odor. *Attention, Perception, & Psychophysics, 76*(6), 1510–1515.

Diego, M. A., Jones, N. A., Field, T., Hernandez-Reif, M., Schanberg, S., Kuhn, C., … & Galamaga, R. (1998). Aromatherapy positively affects mood, EEG patterns of alertness and math computations. *International Journal of Neuroscience, 96*(3–4), 217–224.

Donovan, R., & Rossiter, J. R. (1982). Store atmosphere: An environmental psychology approach. *Journal of Retailing, 58*(1), 34–57.

Doty, R. L., Snyder, P. J., Huggins, G. R., & Lowry, L. D. (1981). Endocrine, cardiovascular, and psychological correlates of olfactory sensitivity changes during the human menstrual cycle. *Journal of Comparative and Physiological Psychology, 95*(1), 45–60.

Duan, X., Tashiro, M., Wu, D. I., Yambe, T., Wang, Q., Sasaki, T., … & Itoh, M. (2007). Autonomic nervous function and localization of cerebral activity during lavender aroatic immersion. *Technology and Health Care, 15*(2), 69–78.

Dux, P. E., & Marois, R. (2009). The attentional blink: A review of data and theory. *Attention, Perception, & Psychophysics, 71*(8), 1683–1700.

Elisabetsky, E., Marschener, J., & Souza, D. O. (1995). Effects of linalool on glutaminergic system in the rat cerebral cortex. *Neurochemistry Research, 20*(4), 461–465.

Goel, N., & Lao, R. P. (2006). Sleep changes vary by odor perception in young adults. *Biological Psychology, 71*(3), 341–349.

Grimes, M. (1999). Helping behavior commitments in the presence of odors: Vanilla, lavender, and no odor. In *National undergraduate research cleaning house* (Vol. 2). Available at: http://www.webclearinghouse.net

Guéguen, N., & Petr, C. (2006). Odors and consumer behavior in a restaurant. *International Journal of Hospitality Management, 25*(2), 335–339.

Herz, R. S. (2009). Aromatherapy facts and fictions: A scientific analysis of olfactory effects on mood, physiology and behavior. *International Journal of Neuroscience, 119*(2), 263–290.

Hirokawa, K., Nishimoto, T., & Taniguchi, T. (2012). Effects of lavender aroma on sleep quality in healthy Japanese students. *Perceptual and Motor Skills, 114*(1), 111–122.

Ho, C., & Spence, C. (2005). Olfactory facilitation of dual-task performance. *Neuroscience Letters, 389*(1), 35–40.

Hommel, B., & Colzato, L. S. (2015). Interpersonal trust: An event-based account. *Frontiers in Psychology, 6,* 1399.

Hommel, B., Colzato, L. S., & Van Den Wildenberg, W. P. (2009). How social are task representations? *Psychological Science, 20*(7), 794–798.

Hongratanaworakit, T. (2004). Physiological effects in aromatherapy. *Songklanakarin Journal of Science and Technology, 26*(1), 117–125.

Hongratanaworakit, T., & Buchbauer, G. (2003). Human behavioral and physiological reactions to inhalation of sweet orange oil. In *III WOCMAP Congress on Medicinal and Aromatic Plants-Volume 5: Quality, Efficacy, Safety, Processing and Trade in Medicinal* (Vol. 679, pp. 75–81).

Hongratanaworakit, T., & Buchbauer, G. (2004). Evaluation of the harmonizing effect of ylang-ylang oil on humans after inhalation. *Planta Medica, 70*(7), 632–636.

Hongratanaworakit, T., Heuberger, E., & Buchbauer, G. (2004). Evaluation of the effects of East Indian sandalwood oil and α-santalol on humans after transdermal absorption. *Planta Medica, 70*(1), 3–7.

Hur, M. H., Song, J. A., Lee, J., & Lee, M. S. (2014). Aromatherapy for stress reduction in healthy adults: A systematic review and meta-analysis of randomized clinical trials. *Maturitas, 79*(4), 362–369.

Iino, H., Miyajim, M., Hara, K., Ohota, K., Matsushima, E., & Matsuura, M. (2011). P300 study on the effects of odors on cognitive function. *Japanese Journal of Aromatherapy, 11,* 52–57.

Ishiguchi, A., Saitou, A., Suenaga, K., Ohta, K., & Matsuura, M. (2008). 14. Effects of odors on electroencephalogram and subjective alterations. *Clinical Neurophysiology, 119*(6), e78.

Janssen, R. H. C., Mattie, H., Plooij-van Gorsel, P. C., & Werre, P. F. (1978). The effects of a depressant and a stimulant drug on the contingent negative variation. *Biological Psychology, 6* (3), 209–218.

Jellinek, J. (1997). Psychodynamic odor effects and their mechanisms. *Perfumer & Flavorist, 22*(5), 29–41.

Jirovetz, L., Buchbauer, G., Jäger, W., Raverdino, V., & Nikiforov, A. (1990). Determination of lavender oil fragrance compounds in blood samples. *Fresenius' Journal of Analytical Chemistry, 338*(8), 922–923.

Johnson, A. J. (2011). Cognitive facilitation following intentional odor exposure. *Sensors, 11*(5), 5469–5488.

Kikuchi, A., Tanida, M., Veboyama, S., Abe, T., & Yamaguchi, H. (1991). Effect of odors in cardiac response patterns in a reaction time task. *Chemical Senses, 16*(2), 183.

Knasko, S. C. (1989). Ambient odor and shopping behavior. *Chemical Senses, 14*(5), 719.

La Torre, M. A. (2003). Aromatherapy and the use of scents in psychotherapy. *Perspectives in Psychiatric Care, 39*(1), 35–37.

Lis-Balchin, M., & Hart, S. (1999). Studies on the mode of action of the essential oil of Lavender (*Lavandula angustifolia* P. Miller). *Phytotherapy Research, 13*(6), 540–542.

Lorig, T. S., & Schwartz, G. E. (1988). Brain and odor: I. Alteration of human EEG by odor administration. *Psychobiology, 16*(3), 281–284.

Manley, C. H. (1993). Psychophysiological effect of odor. *Critical Reviews in Food Science and Nutrition, 33*(1), 57–62.

Meamarbashi, A. (2014). Instant effects of peppermint essential oil on the physiological parameters and exercise performance. *Avicenna Journal of Phytomedicine, 4*(1), 72–78.

Meamarbashi, A., & Rajabi, A. (2013). The effects of peppermint on exercise performance. *Journal of the International Society of Sports Nutrition, 10*(1), 1–6.

Mehrabian, A., & Russell, J. A. (1974). *An approach to environmental psychology*. The MIT Press.

Moeini, M., Khadibi, M., Bekhradi, R., Mahmoudian, S. A., & Nazari, F. (2011). Effect of aromatherapy on the quality of sleep in ischemic heart disease patients hospitalized in intensive

care units of heart hospitals of the Isfahan University of Medical Sciences in 2009. *Iranian Journal of Nursing and Midwifery Research, 15*(4), 234–239.
Moncreiff, R. W. (1966). *Odour preferences*. New York: Wiley.
Morrison, M., Gan, S., Dubelaar, C., & Oppewal, H. (2011). In-store music and aroma influences on shopper behavior and satisfaction. *Journal of Business Research, 64*(6), 558–564.
Moss, M., Cook, J., Wesnes, K., & Duckett, P. (2003). Aromas of rosemary and lavender essential oils differentially affect cognition and mood in healthy adults. *International Journal of Neuroscience, 113*(1), 15–38.
Moss, M., Hewitt, S., Moss, L., & Wesnes, K. (2008). Modulation of cognitive performance and mood by aromas of peppermint and ylang-ylang. *International Journal of Neuroscience, 118*(1), 59–77.
Norrish, M. I. K., & Dwyer, K. L. (2005). Preliminary investigation of the effect of peppermint oil on an objective measure of daytime sleepiness. *International Journal of Psychophysiology, 55*(3), 291–298.
Parasuraman, R., Warm, J. S., & Dember, W. N. (1992). Effects of olfactory stimulation on skin conductance and event-related potentials during visual sustained attention. *Progress Report no. 6 to Fragrance Research Fund*.
Posadzki, P., Watson, L. K., Alotaibi, A., & Ernst, E. (2013). Prevalence of use of complementary and alternative medicine (CAM) by patients/consumers in the UK: Systematic review of surveys. *Clinical Medicine, 13*(2), 126–131.
Raudenbush, B., Corley, N., & Eppich, W. (2001). Enhancing athletic performance through the administration of peppermint odor. *Journal of Sport and Exercise Psychology, 23*(2), 156–160.
Raudenbush, B., Meyer, B., & Eppich, B. (2002). The effects of odors on objective and subjective measures of athletic performance. *International Sports Journal, 6*(1), 14–27.
Raudenbush, B., Grayhem, R., Sears, T., & Wilson, I. (2009). Effects of peppermint and cinnamon odor administration on simulated driving alertness, mood and workload. *North American Journal of Psychology, 11*(2), 245–256.
Raymond, J. E., Shapiro, K. L., & Arnell, K. M. (1992). Temporary suppression of visual processing in an RSVP task: An attentional blink? *Journal of Experimental Psychology: Human Perception and Performance, 18*(3), 849–860.
Rhind, J. P. (2012). *Essential oils: A handbook for aromatherapy practice* (2nd ed.). Singing Dragon.
Roxanaa, O., & Ioan, P. (2013). The effects of ambient scent on consumer behavior: A review of the literature. *Annals of the University of Oradea, Economic Science Series, 22*(1), 1797–1806.
Sakamoto, R., Minoura, K., Usui, A., Ishizuka, Y., & Kanba, S. (2005). Effectiveness of aroma on work efficiency: Lavender aroma during recesses prevents deterioration of work performance. *Chemical Senses, 30*(8), 683–691.
Sebanz, N., Knoblich, G., & Prinz, W. (2003). Representing others' actions: Just like one's own? *Cognition, 88*(3), B11–B21.
Sellaro, R., Hommel, B., Paccani, C. R., & Colzato, L. S. (2015a). With peppermints you're not my prince: Aroma modulates self-other integration. *Attention, Perception, & Psychophysics, 77*(8), 2817–2825.
Sellaro, R., van Dijk, W. W., Paccani, C. R., Hommel, B., & Colzato, L. S. (2015b). A question of scent: Lavender aroma promotes interpersonal trust. *Frontiers in Psychology, 5,* 1486.
Steiner, W., Hanisch, E., & Schwarz, D. (1977). Geruchserlebnis und pupillenerweiterung eine experimentelle untersuchung. *Parfum. & Kosmetik, 58,* 189–196.
Stern, R. M., Ray, W. J., & Quigley, K. S. (2001). *Psychopyhsiological recording*. New York: Oxford University Press.
Sugano, H. (1989). Effects of odors on mental function. *Chemical Senses, 14,* 303.
Sugano, H. (1991). Psychophysiological studies of fragrances. *International Journal of Psychophysiology, 11*(1), 78.
Toda, M., & Morimoto, K. (2008). Effect of lavender aroma on salivary endocrinological stress markers. *Archives of Oral Biology, 53*(10), 964–968.

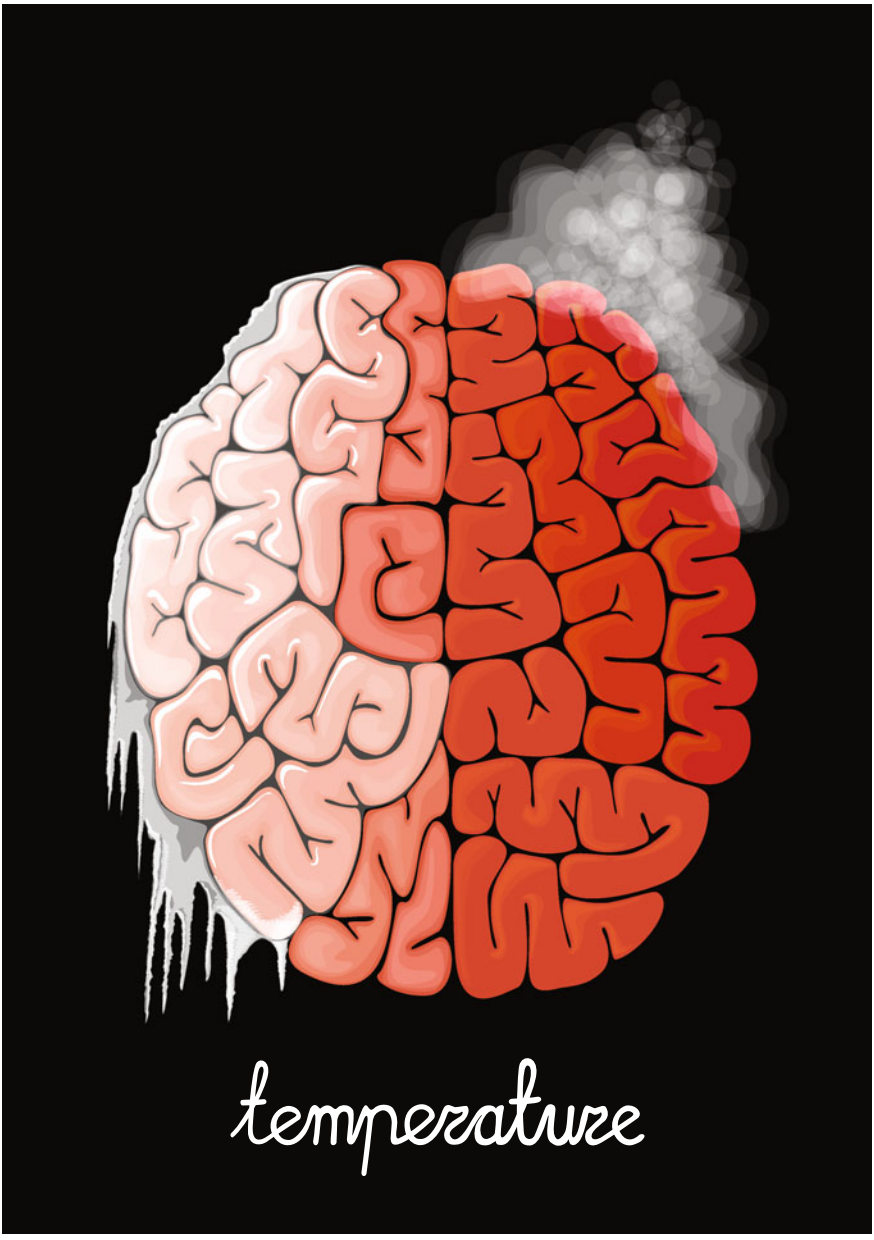
Torii, S., Fukuda, H., Kanemoto, H., Miyanchi, R., Hamauzu, Y., & Kawasaki, M. (1988). Contingent negative variation (CNV) and the psychological effects of odour. In S. Van Toller & G. H. Dodd (Eds.), *Perfumery: The psychology and biology of fragrance* (pp. 107–120). Dordrecht: Springer, Netherlands.

Villemure, C., Slotnick, B. M., & Bushnell, M. C. (2003). Effects of odors on pain perception: Deciphering the roles of emotion and attention. *Pain, 106*(1), 101–108.

Warm, J. S., Dember, W. N., & Parasuraman, R. (1991). Effects of olfactory stimulation on performance and stress. *Journal of the Society Cosmetic Chemists, 42*(3), 199–210.

Watanabe, S., Hara, K., Ohta, K., Iino, H., Miyajima, M., Matsuda, A., … Matsushima, E. (2013). Aroma helps to preserve information processing resources of the brain in healthy subjects but not in temporal lobe epilepsy. *Seizure, 22*(1), 59–63.

Woelk, H., & Schläfke, S. (2010). A multi-center, double-blind, randomised study of the Lavender oil preparation Silexan in comparison to Lorazepam for generalized anxiety disorder. *Phytomedicine, 17*(2), 94–99.


temperature

Temperature

Lorenza S. Colzato, Christina Trepkowski, Roberta Sellaro and Bernhard Hommel

Introduction

"Having warm feelings sitting by someone" or "having cold feet before committing to someone" are two of many commonly used everyday metaphors in which we create connections between the concepts of warmth and affection. Lakoff and Johnson (1999) have suggested an embodied-cognition interpretation of this observation. Abstract feelings may be cognitively represented in terms of (retrieved memories of) concrete experiences, which in turn may refer to previous co-experiences of warmth and affection, or other combinations of perceived temperature affective interpersonal states—with early experiences of infants feeling warm and safe in the arms of their caregiver being a prime example. Representations of co-experienced external and internal events are assumed to be integrated into coherent memory networks or event files (Hommel 2004), so that the re-activation of one element of the resulting episode tends to retrieve the entire episode (Kühn et al. 2011). If so, storing combinations of particular levels of temperature and interpersonal affect would indeed lead to the

L.S. Colzato (✉) · R. Sellaro · B. Hommel
Cognitive Psychology Unit and Leiden Institute for Brain and Cognition, Leiden University, Wassenaarseweg 52, 2333 AK Leiden, The Netherlands
e-mail: colzato@fsw.leidenuniv.nl

L.S. Colzato
Institute of Cognitive Neuroscience, Faculty of Psychology, Ruhr University Bochum, Bochum, Germany

C. Trepkowski
Institute for Experimental Psychology, Heinrich-Heine University Düsseldorf, Düsseldorf, Germany

L.S. Colzato, *Theory-Driven Approaches to Cognitive Enhancement*,
DOI 10.1007/978-3-319-57505-6_18

retrieval of particular temperature representations when in a particular affective state, and to the retrieval of affected-state representations when receiving a particular temperature. Neuroscientific research has also provided evidence for a strong connection between the perception of warmth and affection: the insular cortex is involved in coding both physical and psychological warmth while also being involved in the generation of trust, empathy, and other social emotions (Winston et al. 2002; Decety 2010; Adolphs et al. 2002). These considerations suggest a close bidirectional relationship between temperature perception on the one hand social cognition and action on the other.

In this chapter, we will review the available evidence pertaining to this possible connection and conclude with a brief discussion of the possible mechanisms underlying the effects observed so far.

Affection and Social Proximity

Williams and Bargh (2008; but see Lynott et al. 2015 for a failure to replicate) showed that merely holding a warm, rather than a cold cup is sufficient to induce affection toward others and to judge a target person's personality as warmer. The same kind of manipulation leads persons to feel socially closer to others (IJzerman and Semin 2009), suggesting that temperature somehow impacts the degree of affection and social proximity. These results may have important practical implications when considering for example using temperature manipulations for creating a better working atmosphere. As reported in the introduction, the connection between temperature and social affect seems to be symmetric: the feeling of loneliness is accompanied by both the perception of physical coldness (IJzerman and Semin 2010; Zhong and Leonardelli 2008) and a reduction in body temperature (IJzerman et al. 2012). Szymkow et al. (2013) also showed how the perception of ambient temperature can be influenced by considering communal traits. Communion comprises characteristics that are related to forming and maintaining social connections in contrast to agency traits that are aimed at pursuing personal goals, manifesting skills, and accomplishments. Being primed by negative communion traits (e.g., "rude", "unfriendly", Abele and Wojciszke 2007) in comparison to positive communal qualities (e.g., "honest", "friendly") results in the perception of decreased ambient temperature. This influence on temperature perception is specific for communal traits and not for agency traits, which points to a unique connection between temperature and interpersonal concepts.

The available findings suggest that the link between temperature and social cognition is bidirectional, so that the perception of temperature is affected by social cognition as much as social cognition is affected by temperature. But does this imply that physical warmth and "social warmth" are interchangeable? There is indeed evidence that the increase of one can compensate for shortages of the other. Harlow (1958) was the first to show that interpersonal warmth can be substituted by physical warmth to a certain extent: infant macaques that were reared with a warm

cloth surrogate were less socially damaged by their maternal deprivation than those raised without such warmth. These findings are not limited to animals: Bargh and Shaley (2012) showed that chronic loneliness is associated with a greater tendency to take more frequent, longer, and warmer baths and showers. Thus, also in humans feeling cold and disconnected causes a need for social warmth that can be replaced by physical warmth. These findings may be particularly relevant for therapeutic purposes. In particular, temperature interventions might help to reduce personal and emotional distress especially in elderly people, who suffer from poorer physical and mental health often as a consequence of perceived loneliness and isolation (Chappell and Badger 1989; Tomaka et al. 2006)—independently from, and on top of actual social exclusion (Cornwell and Waite 2009; Tomaka et al. 2006).

The strong association between temperature and social cognition also raised interest in the research area of personal communication. People communicate around the clock and constantly exchange messages with affective content. However, it is still difficult to convey delicate feelings by using common tools only—a smiley or grumpy in a text message will sometimes not fully exploit the emotional range of sender and receiver. Fujita and Nishimoto (2004) reasoned that these difficulties are caused by a lack of real-time awareness of mutual situation, timely action, and nonverbal information processing. They developed "Lovelet", a communication tool, which makes it possible to naturally and timely convey affection with the help of a thermo-sensor. The sensor continuously measures air temperature surrounding one user and transfers these data to the other user. When one user thinks that the other one feels cold a touch sensor can be activated to "warm-up" the other one. This communication tool seems to be an interesting technique to tackle psychological coldness. Indeed, it seems that the power of temperature can be used to directly alter the affective state of someone else. An exciting realization of this idea, which would enable research on this topic in real-life settings, would be the creation of applications for new generations of mobile phones able to send and receive thermal messages and to measure the online reaction of the users.

Similarity and Assimilation

Social proximity, which has been shown to be influenced by temperature, is also connected to the concept of interpersonal similarity insofar as we feel (and often actually are) closer to those who are similar to us (Aron et al. 1991; Hommel et al. 2009; Kim and Hommel 2015). If so, one would expect that warmer temperature leads not only to a closer feeling toward others but also fosters the perception of greater interpersonal similarity, which is indeed what has been observed (Steinmetz and Mussweiler 2011). Recent social comparison research provides evidence that self-other similarity determines whether self-evaluations are assimilated or contrasted toward the other: participants presented with the picture of a strong, muscular man feel stronger in a warmer as compared to a colder environment (Steinmetz and Mussweiler 2011). This suggests that interpersonal similarity

induced by temperature promotes assimilation by attributing the characteristics of the other one to oneself—feature migration in the sense of Ma et al. (2016). These results may be very relevant when considering that manipulating office temperature as an affordable way to promote the assimilation of positive and motivating feelings in working life—which, however, may come with reduced personal responsibility.

Language Use and Attentional Focus

Comparative research has revealed interesting differences in social cognition between members of cultures that emphasize the existence of an independent self, like (North-)Western cultures, and of cultures that rely on a more interdependent concept of self, like in many (East-)Asian cultures (e.g., Nisbett and Miyamoto 2005). The emphasis on independence versus interdependence has been found to be correlated with systematic preferences regarding language use and perceptual focus. Interdependent cultures use more concrete language than independent cultures do (Maass et al. 2006; Semin et al. 2002), which means that action verbs are more likely to be used than state verbs and adjectives. Given that temperature influences social proximity and given the link between social proximity and language use, one would expect that temperature affects language use as well. IJzerman and Semin (2009) confirmed this prediction by showing that people describe film clips in more concrete terms when being exposed to warmer than to colder conditions. This suggests that adopting a concrete communication style in warm temperature could be useful in practical situations that require bargaining, such as sales conversations. Concrete terms do not leave much room for interpretations; they are tangible and easy to understand. Customers know exactly what is meant and will be more likely to remember arguments, because of deeper, more elaborative processing (see Bradshaw and Anderson 1982).

Similar to language use, the link between social proximity and perceptual focus has motivated research on the effect of temperature on attentional focus. Considering that interdependent cultures pay more attention to relations and context (Masuda and Nisbett 2001) while people from independent cultures are rather focused on details and properties (Nisbett and Miyamoto 2005), one would indeed expect that temperature shapes the processing of perceptual information. Indeed, warm temperature has been found to facilitate the processing of perceptual relations when judging the similarity between visual objects (Ijzerman and Semin 2009).

Trust

According to Fiske et al. (2007), people perceived as warm and competent consistently elicit more positive emotions and behavior, while those perceived as lacking warmth and competence elicit negative emotions. Generalizing to

temperature, this suggests that being exposed to warm temperature promotes prosocial behavior. Indeed, catching a warm, as opposed to a cold pack made participants invest more within anonymous partner, suggesting a higher degree of interpersonal trust (Kang et al. 2011). Along the same lines, warm temperature primes made participants to be more likely to choose a gift for a friend than for themselves, whereas cold primes showed the opposite effect (Williams and Bargh 2008). These observations support the idea that the perception of temperature might be related to prosocial behavior. Further support for this idea comes from the finding that activity in the insular cortex was consistently related to both temperature processing and the degree of interpersonal trust (Kang et al. 2011), which suggests that the same neural structures are involved in the perception of warmth and in the generation of trust. The practical implications of these findings may be useful for the setting of psychotherapies treating psychopathological conditions, such as borderline personality disorder, for which difficulties in expressing interpersonal trust play a central role (King-Casas et al. 2008).

Extreme Temperatures

Most of the studies discussed so far have operationalized the warm conditions by choosing room or object temperatures around 23 °C, which means that it is this temperature range that produce the reported greater social proximity, affection, trust, and other positive effects. But what about considerably hotter temperature ranges? Anderson and colleagues (1995) have shown that uncomfortably hot or cold temperatures increase the state of hostility, hostile beliefs, and general negative affect in laboratory studies. In particular, the level of hostility is significantly higher at about 34 or 14 °C as it is at 24 °C, suggesting that very cold or very hot temperature makes people feeling more upset and distressed. Furthermore, data of field studies consistently show that violent crime rates are higher in the South than in other regions of the United States (Anderson 1989). Hotter cities are more violent than cooler cities even after statistically controlling city-to-city differences in Southernness, population size, and socioeconomic status. Time period studies confirm these findings as aggression is higher during hotter days, months, seasons, and years (Anderson et al. 2000, 2001). Even within a time period of a day several studies found increases in assaults, rapes, and domestic violence at hotter temperatures (Anderson et al. 2000). Drivers without air-conditioned cars increase aggressive horn honking (Kenrick and MacFarlane 1986) and at hot temperature police officers are more likely to draw and to use their weapon at least in a simulated burglary scenario with laser training weapons (Vrij et al. 1994). Even though causal interpretations of correlational studies are problematic, these observations may suggest that extreme temperatures are detrimental for social behavior.

Mechanism of Action

Even though a comprehensive theory explaining the available findings is not yet available, the empirical evidence supports the assumption that cognitive representations integrate the features of physical events with the states evoked by them—as suggested by embodied-cognition approaches (e.g., Lakoff and Johnson 1999; for a review, see: Coello and Fischer 2016) and the theory of event coding (TEC: Hommel et al. 2001). Moreover, the available evidence seems to suggest the involvement of four basic cognitive mechanisms or principles.

First, features evoked by encountering one event can be attributed to, and shape the representation of, another event. As demonstrated by the hot- versus cold-cup manipulations of Williams and Bargh (2008) or IJzerman and Semin (2009), an attribute of some external event or condition can "migrate" (Ma et al. 2016) to representations of other events and systematically affect attitudes and actions toward them. This suggests that events are represented in a nonsymbolic, feature-based fashion, and in a way that allows activated feature codes to become part of other representations than the one that is responsible for its activation. This is exactly the representational format claimed by TEC. It assumes that events are represented by networks of feature codes that can refer to physical attributes, affective responses, and overt actions related to an event. TEC distinguishes between the activation of feature codes and their binding into event files (Hommel 2004). The observational feature migration suggests that feature codes that were activated by one event can become bound to another, which would explain why a code representing the warmth of a drink can become part of the representation of another person: as the latter must rely on the current degree of activation of codes, activated codes are more likely to be "mis-bound" into event files they actually do not belong to.

Second, features that were co-perceived in the past are more likely to be co-perceived in other circumstances—so that the previous combination of physical and social warmth leads to the perception of social warmth in the presence of physical warmth, and vice versa. It must be said that the first part of this assumption remains hypothetical in almost all studies on the relationship between temperature and social cognition. That is, the existence of a sufficient number of co-occurrences for the formation of stable episodic memories of these co-occurrences has commonly be assumed rather than been manipulated and tested. More work is necessary to establish this assumption. If it can be established, this would suggest that episodic representations unfold in a kind of pattern-completion logic. That is, representations must consist of several, dissociable components that refer to perceive temperature on the one hand and perceived social features on the other. And these components must be connected in a way that allows some kind of spreading activation from one component to another. This fits with the representational assumptions of TEC, which imply that the co-occurrence of physical warmth and social affection, say, integrates the codes representing these features into event files. Once some external event reactivates one component of an event file, this tends to reactivate the entire file—which has been demonstrated in an fMRI study (Kühn et al. 2011).

Third, the available evidence suggests a systematic impact of temperature on the relationship between self-other similarity (or discrimination) and prosocial cognition and behavior. While the existence of the relationship as such is not new (e.g., Aron et al. 1991), our review suggests warmer temperature increases both self-other similarity and prosocial cognition—either independently or in a causal fashion (e.g., increased self-other similarity may lead to more trust). One interesting implication of this finding is that the degree of self-other integration is rather flexible and can, thus, be affected by situational factors. This supports previous claims that perceived social relatedness is an adaptive state rather than a stable cultural imprint (Kühnen and Oyserman 2002). It also fits with previous observations that the degree of self-other discrimination can be affected by attentional priming (Kühnen and Oyserman 2002; Colzato et al. 2012) and exposure to aromas—with relaxing aromas promoting self-other integration (Sellaro et al. 2015a, b). Sellaro et al. have attributed this observation to the effect of aroma on cognitive-control states and assume that a relaxing aroma induces a more integrative control mode. Along the same lines, we may speculate that warm temperature tends to induce a similar control mode.

Fourth, at least one study suggests that function relating temperature to social cognition and action might not be linear but follow an inverted U shape. That is, prosocial behavior may benefit most from a medium temperature range, as compared to more extreme low- or high-temperature ranges. However, there are two reasons to treat this possibility with great caution. For one, even the one study that was comparing a broader range of temperatures considered only three examples, which in the absence of more systematic studies only allows for a rough categorization. For another, a recent study found subjectively preferred, rather than objective temperature to reliably predict performance in a working memory task (Sellaro et al. 2015a, b). This suggests that, even if there is an inverted U-shaped function relating temperature to prosocial behavior, the peak of this function is likely to differ from person to person. In other words, people may have their own inverted U-shaped function and these functions may not be aligned at the same objective temperature.

Conclusions

All in all, we can conclude that temperature has systematic impact on social cognition and behavior. In general, warm temperature can improve cooperation and interpersonal functioning while (or through) leading to more experienced social proximity and a relational perspective. Fellow humans are perceived as warmer and friendlier and warm temperature fosters interpersonal trust and promotes a more concrete communication style. In contrast, uncomfortably hot or cold temperatures have been found to be detrimental for interpersonal functioning. In any case, there is encouraging preliminary evidence that temperature relates rather systematically to prosocial behavior.

More systematic studies will need to look into more points on the possible temperature range and research in real-life settings will be necessary to determine actual benefits from warmer temperature. For example, the implementation of temperature manipulation in therapeutic for working contexts may be very promising and should be further investigated. Especially the use of physical warmth as substitute for interpersonal warmth seems to be an easy way to partly compensate for loneliness, social exclusion, or related problems, and to promote social collaboration.

References

Abele, A. E., & Wojciszke, B. (2007). Agency and communion from the perspective of self versus others. *Journal of Personality and Social Psychology, 93*(5), 751.

Adolphs, R., Baron-Cohen, S., & Tranel, D. (2002). Impaired recognition of social emotions following amygdala damage. *Journal of Cognitive Neuroscience, 14*(8), 1264–1274.

Anderson, C. A. (1989). Temperature and aggression: Ubiquitous effects of heat on occurrence of human violence. *Psychological Bulletin, 106*(1), 74.

Anderson, C. A., Deuser, W. E., & DeNeve, K. M. (1995). Hot temperatures, hostile affect, hostile cognition, and arousal: Tests of a general model of affective aggression. *Personality and Social Psychology Bulletin, 21*(5), 434–448.

Anderson, C. A., Anderson, K. B., Dorr, N., DeNeve, K. M., & Flanagan, M. (2000). Temperature and aggression. *Advances in Experimental Social Psychology, 32,* 63–129.

Anderson, C. A. (2001). Heat and violence. *Current Directions in Psychological Science, 10*(1), 33–38.

Aron, A., Aron, E. N., Tudor, M., & Nelson, G. (1991). Close relationships as including other in the self. *Journal of Personality and Social Psychology, 60,* 241–253.

Bargh, J. A., & Shalev, I. (2012). The substitutability of physical and social warmth in daily life. *Emotion, 12*(1), 154.

Bradshaw, G. L., & Anderson, J. R. (1982). Elaborative encoding as an explanation of levels of processing. *Journal of Verbal Learning and Verbal Behavior, 21*(2), 165–174.

Chappell, N. L., & Badger, M. (1989). Social isolation and well-being. *Journal of Gerontology, 44* (5), S169–S176.

Coello, Y., & Fischer, M. (Eds.). (2016). *Foundations of embodied cognition*. Hove: Psychology Press.

Colzato, L. S., de Bruijn, E., & Hommel, B. (2012). Up to "me" or up to "us"? The impact of self-construal priming on cognitive self-other integration. *Frontiers in Psychology, 3,* 341.

Cornwell, E. Y., & Waite, L. J. (2009). Social disconnectedness, perceived isolation, and health among older adults. *Journal of Health and Social Behavior, 50*(1), 31–48.

Decety, J. (2010). The neurodevelopment of empathy in humans. *Developmental Neuroscience, 32* (4), 257–267.

Fiske, S. T., Cuddy, A. J., & Glick, P. (2007). Universal dimensions of social cognition: Warmth and competence. *Trends in Cognitive Sciences, 11*(2), 77–83.

Fujita, H., & Nishimoto, K. (2004). Lovelet: A heartwarming communication tool for intimate people by constantly conveying situation data. In *CHI'04 Extended Abstracts on Human Factors in Computing Systems* (pp. 1553–1553). ACM.

Harlow, H. F. (1958). The nature of love. *American Psychologist, 13*(12), 673.

Hommel, B. (2004). Event files: Feature binding in and across perception and action. *Trends in Cognitive Sciences, 8,* 494–500.

Hommel, B., Colzato, L. S., & van den Wildenberg, W. P. M. (2009). How social are task representations? *Psychological Science, 20,* 794–798.

Hommel, B., Müsseler, J., Aschersleben, G., & Prinz, W. (2001). The theory of event coding (TEC): A framework for perception and action planning. *Behavioral and Brain Sciences, 24,* 849–878.

IJzerman, H., Gallucci, M., Pouw, W. T., Weiβgerber, S. C., Van Doesum, N. J., & Williams, K. D. (2012). Cold-blooded loneliness: Social exclusion leads to lower skin temperatures. *Acta Psychologica, 140*(3), 283–288.

IJzerman, H., & Semin, G. R. (2009). The thermometer of social relations mapping social proximity on temperature. *Psychological Science, 20*(10), 1214–1220.

IJzerman, H., & Semin, G. R. (2010). Temperature perceptions as a ground for social proximity. *Journal of Experimental Social Psychology, 46*(6), 867–873.

Kang, Y., Williams, L. E., Clark, M. S., Gray, J. R., & Bargh, J. A. (2011). Physical temperature effects on trust behavior: The role of insula. *Social Cognitive and Affective Neuroscience, 6*(4), 507–515. doi:10.1093/scan/nsq077

Kenrick, D. T., & MacFarlane, S. W. (1986). Ambient temperature and horn honking a field study of the heat/aggression relationship. *Environment and Behavior, 18*(2), 179–191.

Kim, D., & Hommel, B. (2015). An event-based account of conformity. *Psychological Science, 26,* 484–489.

King-Casas, B., Sharp, C., Lomax-Bream, L., Lohrenz, T., Fonagy, P., & Montague, P. R. (2008). The rupture and repair of cooperation in borderline personality disorder. *Science, 321*(5890), 806–810.

Kühn, S., Keizer, A., Colzato, L. S., Rombouts, S. A. R. B., & Hommel, B. (2011). The neural underpinnings of event-file management: Evidence for stimulus-induced activation of, and competition among stimulus–response bindings. *Journal of Cognitive Neuroscience, 23,* 896–904.

Kühnen, U., & Oyserman, D. (2002). Thinking about the self influences thinking in general: Cognitive consequences of salient self-concept. *Journal of Experimental Social Psychology, 38,* 492–499.

Lakoff, G., & Johnson, M. (1999). *Philosophy in the flesh: The embodied mind and its challenge to western thought*. New York: Basic Books.

Lynott, D., Corker, K. S., Wortman, J., Connell, L., Donnellan, M. B., Lucas, R. E., et al. (2015). Replication of "experiencing physical warmth promotes interpersonal warmth" by Williams and Bargh (2008). *Social Psychology, 45*(3), 216–222.

Ma, K., Sellaro, R., Lippelt, D. P., & Hommel, B. (2016). Mood migration: How enfacing a smile makes you happier. *Cognition, 151,* 52–62.

Maass, A., Karasawa, M., Politi, F., & Suga, S. (2006). Do verbs and adjectives play different roles in different cultures? A cross-linguistic analysis of person representation. *Journal of Personality and Social Psychology, 90*(5), 734.

Masuda, T., & Nisbett, R. E. (2001). Attending holistically versus analytically: Comparing the context sensitivity of Japanese and Americans. *Journal of Personality and Social Psychology, 81*(5), 922.

Nisbett, R. E., & Miyamoto, Y. (2005). The influence of culture: Holistic versus analytic perception. *Trends in Cognitive Sciences, 9*(10), 467–473.

Sellaro, R., Hommel, B., Manai, M., & Colzato, L. S. (2015a). Preferred, but not objective temperature predicts working memory depletion. *Psychological Research, 79,* 282–288.

Sellaro, R., Hommel, B., Rossi Paccani, C., & Colzato, L. S. (2015b). With peppermints you're not my prince: Aroma modulates self-other integration. *Attention, Perception, and Psychophysics, 77,* 2817–2825.

Semin, G. R., Görts, C. A., Nandram, S., & Semin-Goossens, A. (2002). Cultural perspectives on the linguistic representation of emotion and emotion events. *Cognition and Emotion, 16*(1), 11–28.

Steinmetz, J., & Mussweiler, T. (2011). Breaking the ice: How physical warmth shapes social comparison consequences. *Journal of Experimental Social Psychology, 47*(5), 1025–1028.

Szymkow, A. C., IJzerman, J., Parchukowski, H., & Wojciszke, M. B. (2013). Warmer hearts, warmer rooms: How positive communal traits increase estimates of ambient temperature. *Social Psychology, 44,* 167–176.

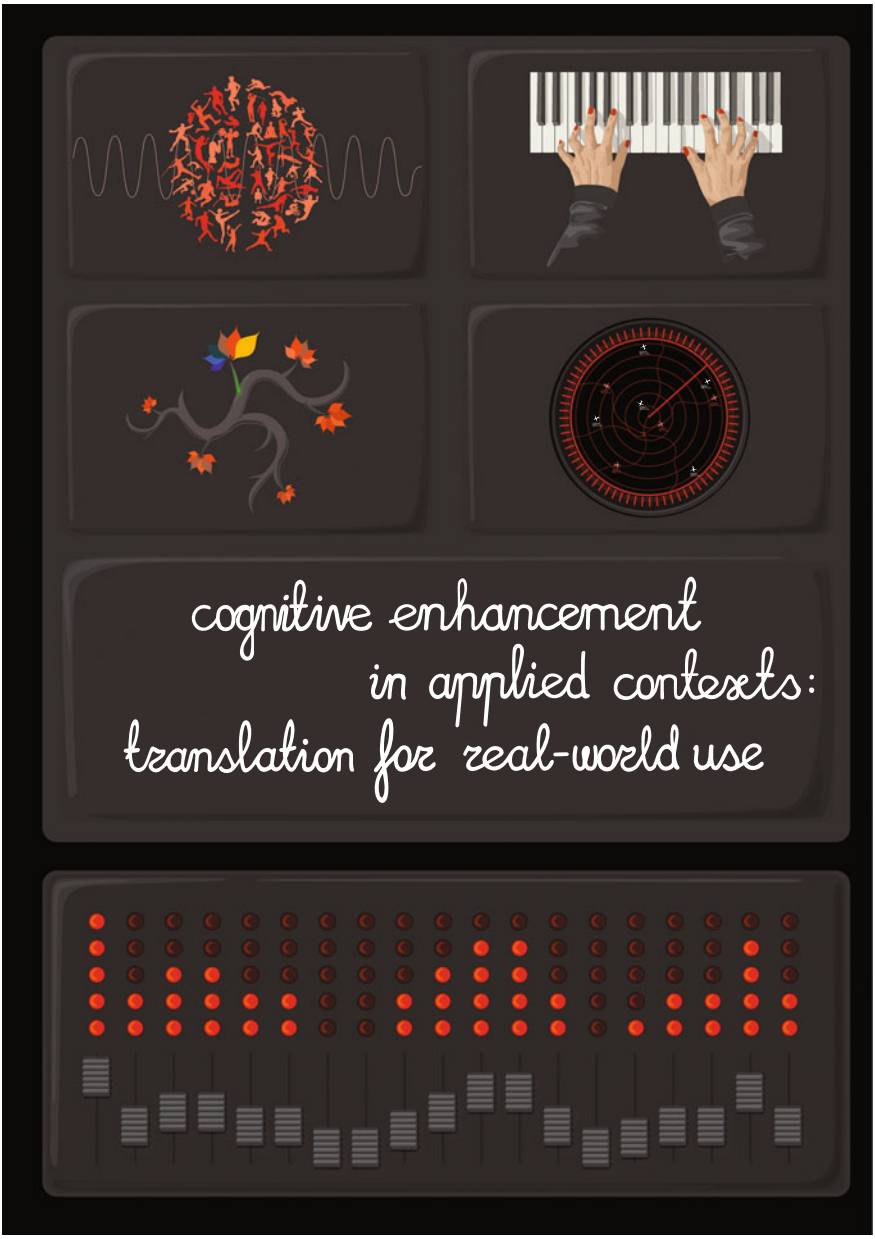
Tomaka, J., Thompson, S., & Palacios, R. (2006). The relation of social isolation, loneliness, and social support to disease outcomes among the elderly. *Journal of Aging and Health, 18*(3), 359–384.

Vrij, A., Van der Steen, J., & Koppelaar, L. (1994). Aggression of police officers as a function of temperature: An experiment with the fire arms training system. *Journal of Community and Applied Social Psychology, 4*(5), 365–370.

Williams, L. E., & Bargh, J. A. (2008). Experiencing physical warmth promotes interpersonal warmth. *Science, 322*(5901), 606–607.

Winston, J. S., Strange, B. A., O'Doherty, J., & Dolan, R. J. (2002). Automatic and intentional brain responses during evaluation of trustworthiness of faces. *Nature Neuroscience, 5*(3), 277–283.

Zhong, C. B., & Leonardelli, G. J. (2008). Cold and lonely does social exclusion literally feel cold? *Psychological Science, 19*(9), 838–842.


cognitive enhancement
in applied contexts:
translation for real-world use

Part VII
Cognitive Enhancement in Applied Contexts—Translation for Real-World Use

Introduction

The present part aims to explore the implementation of cognitive enhancement techniques in applied contexts introduced in the previous chapters. This part will pursue a stronger focus on ecological validity suggesting the need for low-cost and easily accessible intervention programs that translate readily to real-world use. Can active music therapy really help in promoting cognitive improvements in dementia patients? Can the use of brain stimulation make athletes better in identifying the direction of a ball threw to them? Can a profession such as air traffic controllers, which requires the interpretation of multiple data on the radar display, promote our cognition? Considering the steady growth of elderly populations, are online approaches useful interventions to preserve cognitive functions in old age?

Chapter "Musical Activities and Cognitive Enhancement in Dementia" will review the use of music therapy as a tool for improving mood, emotion, and/or cognition in individuals with dementia. In Chapter "The Application of Brain Stimulation and Neural Entrainment in Sport" the term "neurodoping" will be introduced to indicate the use of emerging brain stimulation techniques to enhance physical and mental performance in sports. Chapter "The Case of Air Traffic Control" will consider how a demanding job, such as air traffic control, may represent a unique naturalistic opportunity to investigate how cognition can be shaped and enhanced. Chapter "The Case of the Leiden "Lifestyle 2030" Study" will discuss the experience with implementing *Lifestyle 2030*, a large-scale, Internet-based study at Leiden University investigating older adults consisting of multiple easy-access at-home trainings, such as physical exercise, meditation, learning a new language, and brain training games.


musical activities
and
cognitive enhancement
in dementia

Musical Activities and Cognitive Enhancement in Dementia

Joyce J. de Bruin and Rebecca S. Schaefer

Introduction

Musical activities—either listening passively, or participating actively—have long been applied to health settings, from very uncontrolled paradigms where music is for instance only used to modulate mood in the background, to very specific protocols that directly target symptoms of specific neurological disorders (for instance see the Neurological Music Therapy or NMT program, Thaut 2005). The breadth of possible health applications reflects the range of elements that can be included in musical interactions, which can be featured in an intervention and potentially developed, such as perceptual acuity in pitch or time, individual or joint movement, (nonverbal) affective communication, directing of attention, improvisation, and so on. The element that is crucial to any intervention will thus depend on the problem that is being targeted, and whether the aim is to fully recover, to actively slow decline, or to offer palliative care.

Music therapy is increasingly used for individuals with dementia, based on the idea that musical processing is preserved even though cognitive functions decline over the course of the disease (Baird and Samson 2015). However, in the various stages of impairment, there are wide-ranging individual differences and as such, the level of functioning also clearly determines the kind of intervention or activity that may be both feasible and helpful for a specific patient. In the following, we will focus on the potential effects of music-based interventions on cognitive function in dementia. For the scope of the current discussion, we are interested in effects that are not based on direct practice of a specific function (i.e., using music as a

J.J. de Bruin · R.S. Schaefer (✉)
Health, Medical and Neuropsychology Unit and Leiden Institute for Brain and Cognition, Leiden University, Leiden, The Netherlands
e-mail: r.s.schaefer@fsw.leidenuniv.nl

L.S. Colzato, *Theory-Driven Approaches to Cognitive Enhancement*,
DOI 10.1007/978-3-319-57505-6_19

mnemonic aid), but rather the implications of engaging in a multimodal, hierarchically structured activity to increase cognitive functioning. Here, we discuss passive and active musical interventions of different intensities, looking at single sessions of music listening as well as longer, protocolled interventions.

Music Listening: Incidental or Regular

Cognitive effects of music have been evaluated using single listening sessions, either directly preceding, or played during cognitive tasks as a background stimulus. Additionally, more structured programs of music listening, termed 'passive music therapy', have also been investigated in terms of cognitive improvements.

Brief increases in spatiotemporal abilities were originally reported right after single instances of music listening in healthy young subjects, eventually hypothesized to be driven by music-induced arousal (cf. Rauscher et al. 1993; Nantais and Schellenberg 1999). While the nature and size of this effect are still under some debate (cf. Pietschnig et al. 2010), evidence from small samples of older adults with mild cognitive impairment (MCI, Cacciafesta et al. 2010) and early stage Alzheimer's disease (AD, Johnson et al. 2002) suggests that spatiotemporal abilities can also increase in these groups directly after about 10 min of music listening. Interestingly, individuals with AD who experienced higher impairment in visuospatial tasks seemed to benefit the most from the music listening session, suggesting that this form of musical rehabilitation may also be beneficial for individuals in more progressed stages of AD. Using music as a background stimulus during cognitive tasks has also been reported to have positive effects on healthy elderly (Ferreri et al. 2014; Mammarella et al. 2007), focusing specifically on memory aspects (episodic memory and working memory, respectively), interpreting the increases seen with background music as effects of mood and arousal, but also of an enriched learning context. Small enhancements in category fluency and autobiographical recall were also found for individuals with AD while listening to music as compared to a silent condition (Thompson et al. 2005; Irish et al. 2006). Interestingly, Irish et al. (2006) found no differences in terms of galvanic skin response (GSR) between music and silent conditions, suggesting the cognitive increase was not related to arousal. Conversely, negative effects of background music on memory have also been reported for healthy elderly (Reaves et al. 2015), suggesting that while music may increase arousal and perhaps engagement, music listening also claims attentional resources and can thus be distracting. Although most research into the effects of music listening uses single sessions, an extension of the work on individuals with MCI mentioned above reports that listening to music over a period of 6 months enhanced spatial–temporal abilities without immediate previous listening exposure (Cacciafesta et al. 2010). This implies that repeated music listening may also lead to a more stable cognitive enhancements than those potentially caused by transient increases in arousal. Interestingly, evidence from stroke patients indicates that regular music listening can lead to enhancements in verbal memory and focused

attention, thought to be related to structural reorganization of the brain (Särkämö et al. 2008, 2014), suggesting that the longer term effectivity of passive music therapy greatly depends on the potential for neural adaptation.

In sum, a single music listening sessions may enhance several cognitive skills, thought to be driven by an arousal response, although this idea has not been supported directly. Moreover, the patient samples tend to be limited, and potentially relevant aspects of the music—emotional qualities, liking, familiarity for the listener, etc.—have not been formally investigated. As such, various elements of music listening need further assessment, namely which aspects of the chosen musical pieces may increase arousal or enhance cognition, which cognitive skills may be enhanced, the timescale at which this enhancement may take place, and which clinical populations can benefit. Regular music listening may enhance cognitive skills in individuals with dementia, but more research is necessary to support this assertion and assess the therapy characteristics (e.g., how many sessions, or type of music) that may create the optimal outcome.

Active Music Therapy

Active music therapy requires the participant to interact with the music, for instance by singing or playing an instrument. Although a number of meta-analyses indicate that active music therapy is effective in lowering agitation and improving mood, effects on cognitive improvements in dementia patients are generally very small, or quite specific to the trained task (Chang et al. 2015; Ueda et al. 2013 Vasionytė and Madison 2013), and not seen for healthy elderly (Li et al. 2015). The different meta-analyses varied in their inclusion criteria, indicating a weakness in this approach. While single music listening sessions show promising results in terms of cognitive increases, longer interventions appear to lead to improvement in specific functions rather than general cognition. For instance, individuals with AD who sang songs and discussed its content showed an enhancement in speech content and fluency but not in general cognition, when compared to participants of speech therapy (Brotons and Koger 2000). Participating in singing training minimally three times a week with the use of songs from their youth and a karaoke machine in a small group of individuals with mild/moderate AD led to enhanced psychomotor speed, but no difference in more general cognitive measures such as the Mini-Mental State Examination (MMSE), word fluency, or memory (Satoh et al. 2015). Conversely, a small group of individuals with dementia who sang or played percussion instruments showed enhancements in language skills, but not in general cognition (Suzuki et al. 2004). However, methodologically stronger studies, which include larger sample sizes and active control groups (receiving another form of therapy), tend not to replicate these results. A weekly therapy for individuals with moderate to severe AD that consisted of listening and singing/playing percussion found no short- or long-term enhancements in cognition (Narme et al. 2014), although emotional state was markedly improved.

Intuitively, it appears that passive (i.e., listening) and active (i.e., participating) activities might differ substantially, but for individuals with mild to moderate AD, both a therapy comprising singing along with familiar songs, and therapy based on listening to familiar songs and trying to remember past events improved general cognition, attention, and executive functioning. However, the active therapy also temporarily enhanced short-term memory and working memory. For both therapies a long-term enhancement was found in orientation compared to a control group (Särkämö et al. 2013). Although cognitive functions were not tested specifically, clapping or singing along with music enhanced general functioning more than passively listening to a music recording, but this increase was only maintained when the therapy was continued (Sakamoto et al. 2013). Two multi-element music therapies, which are arguably more challenging and engaging, found (short-term) enhancements in general cognition in individuals with AD and either consisted of songwriting elements (e.g., creating lyrics/melodies) and actively remembering past events and social contact (Hong and Choi 2011) or consisted of listening, singing, playing an instrument, stimulating other senses, telling jokes, and encouragement of laughter (Bruer et al. 2007). For these therapies, it remains unclear what element caused the cognitive enhancement, but it underlines an important issue regarding the complexity and richness of the intervention activities.

Taken together, the support for the increase of cognitive function in dementia can be said to be patchy at best, but isolated cases show substantial potential, with increased effects for more complex interventions. While some meta-analyses do make distinctions between passive and active involvement, or even specific intervention elements (cf. Ueda et al. 2013, who separate listening, singing, rhythm, and improvisation-based methods), it is difficult to compare studies due to diverse forms of therapies used. Additional to active or passive engagement, group or individual therapy, use of autobiographical memories or music preference, and the involvement of a trained music therapist are sometimes considered as relevant features. Importantly, the control interventions that are chosen as comparisons can speak to the uniqueness of music in enhancing cognition, and the findings do not suggest that music is necessarily more effective than other cognitively stimulating activities, with multisensory stimulation ('Snoezelen') showing similar and sometimes better results than music interventions (cf. Sánchez et al. 2016; Strøm et al. 2016). Finally, the main effects of music therapy on individuals with dementia appear to target mood and emotion, which of course could in turn also be at the basis of cognitive effects. Therefore, continuing investigations are necessary in order to identify elements of music therapy that may directly affect cognition.

Conclusion

Music therapy in its various forms is a promising tool to enhance cognitive skills that are not specifically trained by the therapy, due to the potential richness of the activities involved. However, research is scarce, effects on cognition are often small

and most studies contain methodological limitations, such as small sample sizes, lack of longitudinal data or active control groups (Chang et al. 2015; Young et al. 2016). Also, studies often differ in included intervention elements, making it impossible to compare them, thus reducing the value of meta-analytic approaches. Furthermore, as music therapy is often found to reduce disruptive behavior and anxiety level or enhance mood (Chang et al. 2015), mood enhancement may also mediate between music therapy and cognitive enhancement by influencing arousal/attention.

Findings outside the current scope suggest not only that music can be used as a mnemonic aid in dementia patients (cf. Moussard et al. 2014; Simmons-Stern et al. 2012), but also that playing music regularly reduces the chance of developing the clinical symptoms of dementia (Grant and Brody 2004; Stern 2012; Verghese et al. 2003; Wan and Schlaug 2010). These findings suggest that musical activities can impact the clinical expression of brain damage, potentially through increased neural connectivity and task flexibility, and can still be a valuable tool for individuals with neurological disorders. As such, we can consider music therapy a promising way to enhance cognitive skills either directly or through task transfer, but more methodologically valid research is necessary that takes into consideration the characteristics of the patient, the stage and characteristics of the disorder, the elements of the musical therapy, and the possible influence of mood enhancement.

References

Baird, A., & Samson, S. (2015). Music and dementia. *Progress in Brain Research, 217,* 207–235.

Brotons, M., & Koger, S. M. (2000). The impact of music therapy on language functioning in dementia. *Journal of Music Therapy, 37,* 183–195.

Bruer, R. A., Spitznagel, E., & Cloninger, C. R. (2007). The temporal limits of cognitive change from music therapy in elderly persons with dementia or dementia-like cognitive impairment: A randomized controlled trial. *Journal of Music Therapy, 44,* 308–328.

Cacciafesta, M., Ettorre, E., Amici, A., Cicconetti, P., Martinelli, V., Linguanti, A., et al. (2010). New frontiers of cognitive rehabilitation in geriatric age: The Mozart effect (ME). *Archives of Gerontology and Geriatrics, 51,* 79–82.

Chang, Y., Chu, H., Yang, C., Tsai, J., Chung, M., Liao, Y., et al. (2015). The efficacy of music therapy for people with dementia: A meta-analyses of randomized controlled trials. *Journal of Clinical Nursing, 24,* 3425–3440.

Ferreri, L., Bigand, E., Perrey, S., Muthalib, M., Bard, P., & Bugaiska, A. (2014). Less effort, better results: How does music act on prefrontal cortex in older adults during verbal encoding? An fNIRS study. *Frontiers in Human Neuroscience, 8*(5), 301.

Grant, M. D., & Brody, J. A. (2004). Musical experience and dementia. Hypothesis. *Aging Clinical and Experimental Research, 16,* 403–405.

Hong, I. S., & Choi, M. J. (2011). Songwriting oriented activities improve the cognitive functions of the aged with dementia. *The Arts in Psychotherapy, 38,* 221–228.

Irish, M., Cunningham, C. J., Walsh, J. B., Coakley, D., Lawlor, B. A., Robertson, I. H., et al. (2006). Investigating the enhancing effect of music on autobiographical memory in mild Alzheimer's disease. *Dementia and Geriatric Cognitive Disorders, 22*(1), 108–120.

Johnson, J. K., Shaw, G. L., Vuong, M., Vuong, S., & Cotman, C. W. (2002). Short-term improvement on a visual-spatial task after music listening in Alzheimer's Disease. *Activities, Adaptation and Aging, 26*(3), 37–50.

Li, H. C., Wang, H. H., Chou, F. H., & Chen, K. M. (2015). The effect of music therapy on cognitive functioning among older adults: A systematic review and meta-analysis. *Journal of the American Medical Directors Association, 16*(1), 71–77.

Mammarella, N., Fairfield, B., & Cornoldi, C. (2007). Does music enhance cognitive performance in healthy older adults? The Vivaldi effect. *Aging Clinical and Experimental Research, 19*(5), 394–399.

Moussard, A., Bigand, E., Belleville, S., & Peretz, I. (2014). Learning sung lyrics aids retention in normal ageing and Alzheimer's disease. *Neuropsychological Rehabilitation, 24,* 894–917.

Nantais, K. M., & Schellenberg, E. G. (1999). The Mozart effect: An artifact of preference. *Psychological Science, 10*(4), 370–373.

Narme, P., Clément, S., Ehrlé, N., Schiaratura, L., Vachez, S., Courtaigne, B., et al. (2014). Efficacy of musical interventions in dementia: Evidence from a randomized controlled trial. *Journal of Alzheimer's Disease, 38*(2), 359–369.

Pietschnig, J., Voracek, M., & Formann, A. K. (2010). Mozart effect-Shmozart effect: A meta-analyses. *Intelligence, 38,* 314–323.

Rauscher, F. H., Shaw, G. L., & Ky, K. N. (1993). Music and spatial task performance. *Nature, 365,* 611.

Reaves, S., Graham, B., Grahn, J., Rabannifard, P., & Duarte, A. (2015). Turn off the music! Music impairs visual associative memory performance in older adults. *The Gerontologist*, gnu113.

Sakamoto, M., Ando, H., & Tsutou, A. (2013). Comparing the effects of different individualized music interventions for elderly individuals with severe dementia. *International Psychogeriatrics, 25,* 775–784.

Särkämö, T., Tervaniemi, M., Laitinen, S., Forsblom, A., Soinila, S., Mikkonen, M., et al. (2008). Music listening enhances cognitive recovery and mood after middle cerebral artery stroke. *Brain, 131,* 866–876.

Särkämö, T., Tervaniemi, M., LicPhil, S. L., Numminen, A., Kurki, M., Johnson, J. K., et al. (2013). Cognitive, emotional, and social benefits of regular musical activities in early dementia: Randomized controlled study. *The Gerontologist, 54,* 634–650.

Särkämö, T., Ripolles, P., Vepsalainen, H., Autti, T., Silvennoinen, H. M., Salli, E., et al. (2014). Structural changes induced by daily music listening in the recovering brain after middle cerebral artery stroke: A voxel-based morphometry study. *Frontiers in Human Neuroscience, 8,* 1–16.

Sánchez, A., Marante-Moar, M. P., Sarabia, C., de Labra, C., Lorenzo, T., Maseda, A., et al. (2016). Multisensory stimulation as an intervention strategy for elderly patients with severe dementia a pilot randomized controlled trial. *American Journal of Alzheimer's Disease and Other Dementias, 31*(4), 341–350.

Satoh, M., Yuba, T., Tabei, K., Okubo, Y., Kida, H., Sakuma, H., et al. (2015). Music therapy using singing training improves psychomotor speed in patients with Alzheimer's disease: A neuropsychological and fMRI study. *Dementia and Geriatric Cognitive Disorders Extra, 5,* 296–308.

Simmons-Stern, N. R., Deason, R. G., Brandler, B. J., Frustace, B. S., O'Connor, M. K., Ally, B. A., et al. (2012). Music-based memory enhancement in Alzheimer's Disease: Promise and limitations. *Neuropsychologia, 50*(14), 3295–3303.

Strøm, B. S., Ytrehus, S., & Grov, E. K. (2016). Sensory stimulation for persons with dementia: A review of the literature. *Journal of Clinical Nursing, 25*(13–14), 1805–1834.

Suzuki, M., Kanamori, M., Watanabe, M., Nagasawa, S., Kojima, E., Ooshiro, H., et al. (2004). Behavioral and endocrinological evaluation of music therapy for elderly patients with dementia. *Nursing and Health Sciences, 6,* 11–18.

Stern, Y. (2012). Cognitive reserve in ageing and Alzheimer's disease. *The Lancet Neurology, 11,* 1006–1012.

Thaut, M. H. (2005). *Rhythm, music, and the brain: Scientific foundations and clinical applications.* London: Routledge.

Thompson, R. G., Moulin, C. J. A., Hayre, S., & Jones, R. W. (2005). Music enhances category fluency in healthy older adults and Alzheimer's disease patients. *Experimental Aging Research, 31,* 91–99.

Ueda, T., Suzukamo, Y., Sato, M., & Izumi, S. I. (2013). Effects of music therapy on behavioral and psychological symptoms of dementia: A systematic review and meta-analysis. *Ageing research reviews, 12*(2), 628–641.

Vasionytė, I., & Madison, G. (2013). Musical intervention for patients with dementia: A meta-analysis. *Journal of Clinical Nursing, 22*(9–10), 1203–1216.

Verghese, J., Lipton, R. B., Katz, M. J., Hall, C. B., Derby, C. A., Kuslansky, G., et al. (2003). Leisure activities and the risk of dementia in the elderly. *The New England Journal of Medicine, 348,* 2508–2516.

Wan, C. Y., & Schlaug, G. (2010). Music making as a tool for promoting brain plasticity across the lifespan. *The Neuroscientist, 16,* 566–577.

Young, R., Camic, P. M., & Tischler, V. (2016). The impact of community-based and health interventions on cognition in people with dementia: A systematic literature review. *Aging and Mental Health, 20,* 337–351.

application of brain stimulation and neural entrainment in sports

The Application of Brain Stimulation and Neural Entrainment in Sport

Lorenza S. Colzato, Carlotta Stern and Armin Kibele

Introduction

Citius, altius, fortius—faster, higher, stronger—these three adjectives incorporate the spirit of competitive sport, not only for professional but also for amateur athletes. The huge pressure exerted by trainers on athletes to enhance performance and "to be on top" all the time has raised the interest in boosting performance using new methods and materials. In recent years, the application of nonpharmacological brain stimulation and neural entrainment techniques in sport science has become increasingly popular as a topic of scientific research because of their enhancing effects on athletic performance. Theoretically, brain stimulation techniques, such as transcranial direct current stimulation (tDCS), and neural entrainment techniques, such as neurofeedback, transcranial alternating current stimulation (tACS) and binaural beats, operate on different mechanisms of action. Whereas, tDCS modifies brain excitability through weak, direct electric currents (see also Chapter "Transcranial Direct Current Stimulation"), tACS (see Chapter "Transcranial Alternating Current Stimulation"), neurofeedback (see Chapter "Neurofeedback")

L.S. Colzato (✉)
Cognitive Psychology Unit and Leiden Institute for Brain and Cognition, Leiden University, Leiden, The Netherlands
e-mail: colzato@fsw.leidenuniv.nl

C. Stern
Department of Psychology, University of Kassel, Kassel, Germany

A. Kibele
Institute for Sports and Sport Science, University of Kassel, Kassel, Germany

L.S. Colzato
Faculty of Psychology, Institute of Cognitive Neuroscience, Ruhr University Bochum, Bochum, Germany

L.S. Colzato, *Theory-Driven Approaches to Cognitive Enhancement*,
DOI 10.1007/978-3-319-57505-6_20

and binaural beats (see also Chapter "Binaural Beat Stimulation") are techniques by means of which the brain "takes over" or synchronises its activity on the base of external or internal stimulation. Recently Davis (2013) has coined the term "neurodoping" to indicate the use of these emerging techniques to enhance physical and mental performance in sports. Indeed, factors which are considered crucial to athletic performance, such as motor learning, enhanced muscular strength or reduced fatigue, or even speeding up the learning rate in specific motor skills or better sleeping quality can be promoted by the use of brain stimulation and neural entrainment techniques.

In this chapter, adapted from Colzato et al. (2017), we will first describe the available studies investigating how brain stimulation can increase athletic performance. Second, we will review studies exploring the beneficial effect of neural entrainment on various sports. The studies indicate that these emerging techniques are promising and legitimate tools to enhance physical and mental performances in sports.

Improvements in Muscular Strength, Motion Perception, Motor Learning and Muscle Fatigue Through Brain Stimulation

The effects of noninvasive brain stimulation procedures, such as tDCS, on athletic performance have been investigated in several studies. In this section, we will give an overview about recent findings on muscular strength, motion perception, motor learning and muscle fatigue. In particular, we will refer to two stimulation conditions. First, the anodal stimulation which causes a slight depolarization of the resting membrane potential, increases the probability of neural firing and, consequently, enhances cortical excitability. Second, the cathodal stimulation leading to a slight hyperpolarization of the resting membrane potential and hence to decreased probability of neural firing rates and excitability (see Chapter "Transcranial Direct Current Stimulation").

Cogiamanian et al. (2007) examined the effects of tDCS on neuromuscular fatigue in submaximal isometric contractions of the left elbow in 24 healthy participants (who did not participate in competitive sports). The authors found a significant decrease in the neuromuscular fatigue of 15% when anodal tDCS was applied over the motor areas of the scalp. This outcome suggests that anodal tDCS can improve muscle performance and decrease muscle fatigue. Additional evidence for an enhancement of muscle endurance comes from a study in which sustained submaximal contractions of the elbow flexion was examined in 18 healthy participants (Williams et al. 2013). During fatigue task performance, either anodal or sham stimulation was administered to the motor cortex for up to 20 min. The results indicate that anodal stimulation increased time to task failure and the amount of muscle fatigue, suggesting that the administration of tDCS during performance of

fatiguing activity is able to augment the capability to exercise under challenging conditions (Williams et al. 2013). Further, a recent study investigated the effect of anodal tDCS on perceived exertion, heart rate and performance outcome during a maximal incremental cycling protocol in ten experienced male cyclists (Okano et al. 2013). Anodal tDCS was positioned over the left temporal cortex because this brain area is associated with autonomic nervous system control and previous evidence has shown that its stimulation was successful in modulating this system (Montenegro et al. 2011). The stimulation resulted in a slower increase of perceived exertion during exercise. Moreover, peak power output (highest intensity a cyclist can sustain for more than 1 min) was increased by 4% with heart rates reduced at submaximal workloads (Okano et al. 2013). Similarly, Vitor-Costa et al. (2015) investigated the enhancing effect of tDCS over the primary motor cortex on muscle fatigue and exercise tolerance in 11 cyclists. Anodal tDCS produced enhanced performance in the time to exhaustion at 80% of peak power. However, no significant effect were found in perceived exertion and heart rate indicating that anodal tDCS selectively enhanced performance without affecting physiological and perceptual variables.

Aside from the beneficial effect on muscle fatigue, a recent study has shown an enhancing effect of tDCS on implicit motor learning through a stimulation procedure over the left dorsal–lateral prefrontal cortex (Zhu et al. 2015). Here, cathodal tDCS and sham stimulation were compared in 27 healthy participants showing improvements in golf putting while verbal working memory was impaired. The authors suggest that the suppression of verbal working memory induced by cathodal tDCS induced impairments in explicit control strategies and consequently promoted implicit motor learning of the golf putting skill. Earlier, the effects of noninvasive cortical stimulation were studied on the extended time course of learning a novel and challenging motor skill task (Reis et al. 2009). Two groups of 12 subjects practiced over 5 consecutive days while receiving tDCS over the primary motor cortex. Within-day and between-day effects and on the rate of forgetting during a 3-month follow-up were examined. There was greater total skill acquisition with anodal tDCS compared to sham. Anodal tDCS did not change the rate of forgetting relative to sham across the 3-month follow-up period, and consequently the skill measure remained greater with anodal tDCS at 3 months.

Finally, tDCS of the visual cortex was found to improve motion perception in visuomotor tracking task (Antal et al. 2004). Here, 12 participants received cathodal and anodal stimulation over different areas in the visual cortex and the motor cortex. The percentage of correct tracking movements increased specifically during and immediately after cathodal stimulation of an area responsible for motion perception only while no effects were found for the other stimulation conditions.

In summary, from the above studies, tDCS seems to be a promising tool to enhance muscular strength, motion perception, motor learning and fatigue all crucial for athletic performance.

Improvements in Motor Sequence Learning and Motor Skill Learning Through Neural Entrainment Procedures

In this section, studies will be reviewed investigating the effects of neural entrainment procedures on athletic performance including tACS, neurofeedback and binaural beats. The idea behind neural entrainment is that the rhythmic oscillatory activity within and between different brain regions is considered to play a causal role in a wide range of cognitive functioning.

Similar to tDCS, tACS protocols employ weak electrical current to the scalp through two or more electrodes placed over brain areas of interest. However, while tDCS is used to induce a constant current flow, tACS is used to apply an oscillatory (sinusoidal) electrical stimulation of a specific frequency to modulate neuronal membrane potentials in a frequency-dependent manner (see Chapter "Transcranial Alternating Current Stimulation"). Recently, Pollok et al. (2015) investigated the effects of tACS when employed over the left primary motor cortex within the alpha and beta frequency bands on motor sequence learning as indexed by a serial reaction time task (SRTT). Results in 26 participants show that SRTT significantly improved at 10 and 20 Hz-tACS. This outcome indicates that tACS facilitates sequence learning and promotes quicker skill acquisition.

In contrast to tACS, neurofeedback training provides individuals with real-time information about their level of cortical activity via sounds or visual displays. In this respect, cortical activity may be entrained, changed or regulated prior to or during physical activity (see Chapter "Neurofeedback"). In one of the first studies on the impact of such EEG-biofeedback procedures on athletic performance, 24 pre-elite archers were examined (Landers et al. 1991). Two groups were tested based on previous evidence showing that (1) situations requiring attention and preparation elicit slow brain potentials (Rockstroh et al. 1982) and (2) reduced EEG activity in the left temporal cortex was associated with better sport performance (Hatfield et al. 1984). Therefore, one group received biofeedback designed to augment left temporal low-frequency activity (correct biofeedback) and the other group received feedback to augment instead right temporal low-frequency activity (incorrect biofeedback). The results revealed that the archers who received correct biofeedback compared to incorrect or no biofeedback training significantly improved performance while no effects were observed in self-reported measures of concentration and self-confidence. In another study, effects of real-life neurofeedback training on golf performance was examined by Arns and colleagues (Arns et al. 2008). A personal event-locked EEG profile at frontopolar site (FPz) was calculated for successful versus unsuccessful putts in six amateur golfers. Target frequency bands and amplitudes marking optimal prefrontal brain state were derived from the profile and based on these parameters individual neurofeedback training was applied. These authors measured brain activities in six amateur golfers during successful putts. The overall percentage of successful putts was significantly larger when feedback was provided as compared to a no-feedback condition. All in all, participants improved their putting performance with neurofeedback related to

their personalized EEG profile by an average of 25%. Similarly, in a recent study, Ring et al. (2015) examined neurofeedback procedures at frontal site (Fz) in 24 golfers to regulate brain activity towards a reduction of their frontal high-alpha power as a prerequisite prior to successful putting performance. Alpha power was chosen based on previous findings that voluntary self-paced movements (such as golf putts) are preceded by a reduction (i.e., desynchronisation) in EEG alpha power (Leocani et al. 1997). Fz site was relevant because this site was found to capture the strongest differences in high-alpha power between experts and novices and successful and unsuccessful outcomes in the moments preceding golf putts (Cooke et al. 2014). The findings showed that neurofeedback training was successful in reducing the golfers alpha-band activity while no improvements were found in the putting performance. In a similar study, but without a control group and with a very low sample size, a pre-post intervention of neurofeedback training was conducted to decrease the frontal midline theta amplitude in three highly skilled male golfers (Kao et al. 2014). Low theta-band activity is considered a prerequisite for optimal top–down control and sustained attention. Putting scores and scoring stability improved and the golfers exhibited lower frontal midline theta amplitude during the resting condition following neurofeedback training, pointing out that the tonic reduction of frontal midline theta amplitude may play a role in subsequent performance enhancement. Aside from golf putting studies, beneficial effects of neurofeedback training were shown in rifle shooters as well. Here, expert shooter were asked to maintain intermediate-frequency EEG bandwidths (sensorimotor rhythm and alpha-band) while inhibiting high- and low-frequency bandwidths (theta and high beta) for at least 80% of the practice duration (Rostami et al. 2012). The results revealed improvements of shooting performance when compared to a control group. That is, consolidating low-frequency brain activity can be useful for improving rifle shooting performance.

Similar to tACS, binaural beats may be used for brainwave entrainment as well. However, whereas tACS is used to apply an oscillatory (sinusoidal) electrical stimulation of a specific frequency, the entrainment via binaural beats is employed by presenting two beats of slightly different frequency (for instance 300 and 340 Hz) through headphones. As a result, the individual detects a single beat only that differs in amplitude at a frequency equal to difference between the two presented beats (40 Hz). The basic assumption is that listening to binaural beats in a specific frequency band will entrain the same frequency in the brain (see Chapter "Binaural Beat Stimulation"). Recently, this effect has been investigated for delta-band (2–8 Hz) in order to affect sleeping quality in 15 young elite soccer players (Abeln et al. 2014). During a period of eight weeks, participants' beds were equipped with integrated sound systems embedded in the pillows to employ the binaural beat effect. As a consequence, sleep diaries, self-assessment questionnaires and mood ratings showed significant improvements in sleep and awakening quality.

All in all, these results show that neural entrainment through tACS, neurofeedback and binaural beats can speed up the learning of motor skills in sports, boosts motor sequence learning, and enhances sleeping quality to promote optimal performance during competition.

Conclusion

Brain stimulation and neural entrainment have the potential to enhance athletic performance.

Even though some studies lack ecological validity towards sports and other studies reported very small sample sizes, it seems plausible that these emerging techniques will be a future, legitimate way to enhance physical and mental performance in sports. As pointed out by Davis (2013), the application of these techniques in sport science raises ethical concerns about neurodoping in sport. Notably, brain stimulation and neural entrainment may be considered as an artificial supplement to normal training in sports provoking ethical debates about its application. In accordance to Davis (2013), if used according safety protocols, we believe that neuro-enhancement during training should not be considered to be unethical and illicit in sport. However, it is important to acknowledge that extensive research is needed to verify whether the observed brain stimulation and neural entrainment-induced changes in athletic performance are preserved over time. Previous studies on cognitive functioning have suggested that repetitive sessions of tDCS can increase the effects of stimulation (Nitsche and Paulus 2011), but it remains to be established whether the same applies to athletic performance. Hence, future studies assessing the impact of multiple stimulation sessions and the risk of incurring potential side-effects are necessary. Moreover, optimal protocols of stimulation (e.g., intensity and duration of the stimulation, online vs. offline stimulation, electrode size and number, scalp placement) still need to be identified. Further, in order to find unequivocal evidence that these emerging techniques improve athletic performance, homogeneity across different studies also in terms of study design and the specific task/questionnaire used is mandatory.

Although more research is needed to fully understand the effects brain stimulation and neural entrainment on athletic performance, we conclude that these emerging techniques are promising tools to enhance athletic performance such as motor learning, muscular strength, increased learning rate in specific motor skills, sleep and fatigue.

References

Abeln, V., Kleinert, J., Strüder, H. K., & Schneider, S. (2014). Brainwave entrainment for better sleep and post-sleep state of young elite soccer players—A pilot study. *European Journal of Sport Science, 14*(5), 393–402.

Antal, A., Nitsche, M. A., Kruse, W., Kincses, T. Z., Hoffmann, K. P., & Paulus, W. (2004). Direct current stimulation over V5 enhances visuomotor coordination by improving motion perception in humans. *Journal of Cognitive Neuroscience, 16*(4), 521–527.

Arns, M., Kleinnijenhuis, M., Fallahpour, K., & Breteler, R. (2008). Golf performance enhancement and real-life neurofeedback training using personalized event-locked EEG profiles. *Journal of Neurotherapy, 11*(4), 11–18.

Cogiamanian, F., Marceglia, S., Ardolino, G., Barbieri, S., & Priori, A. (2007). Improved isometric force endurance after transcranial direct current stimulation over the human motor cortical areas. *European Journal of Neuroscience, 26*(1), 242–249.

Colzato L. S., Nitsche, M. A., & Kibele, A. (2017). Non-invasive brain stimulation and neural entrainmentt enhance athletic performance: A review. *Journal of Cognitive Enhancement.*

Cooke, A., Kavussanu, M., Gallicchio, G., Willoughby, A., McIntyre, D., & Ring, C. (2014). Preparation for action: Psychophysiological activity preceding a motor skill as a function of expertise, performance outcome, and psychological pressure. *Psychophysiology, 51*(4), 374–384.

Davis, N. J. (2013). Neurodoping: Brain stimulation as a performance-enhancing measure. *Sports Medicine, 43*(8), 649–653.

Hatfield, B. D., Landers, D. M., & Ray, W. J. (1984). Cognitive processes during self-paced motor performance: An electroencephalographic profile of skilled marksmen. *Journal of Sport Psychology, 6*(1), 42–59.

Kao, S. C., Huang, C. J., & Hung, T. M. (2014). Neurofeedback training reduces frontal midline theta and improves putting performance in expert golfers. *Journal of Applied Sport Psychology, 26*(3), 271–286.

Landers, D. M., Petruzzello, S. J., Salazar, W., Crews, D. J., Kubitz, K. A., Gannon, T. L., et al. (1991). The influence of electrocortical biofeedback on performance in pre-elite archers. *Medicine and Science in Sports and Exercise, 23*(1), 123–129.

Leocani, L., Toro, C., Manganotti, P., Zhuang, P., & Hallett, M. (1997). Event-related coherence and event-related desynchronization/synchronization in the 10 Hz and 20 Hz EEG during self-paced movements. *Electroencephalography and Clinical Neurophysiology/Evoked Potentials Section, 104*(3), 199–206.

Montenegro, R. A., Farinatti, P. D. T. V., Fontes, E. B., da Silva Soares, P. P., da Cunha, F. A., Gurgel, J. L., … Okano, A. H. (2011). Transcranial direct current stimulation influences the cardiac autonomic nervous control. *Neuroscience Letters*, *497*(1), 32–36.

Nitsche, M. A., & Paulus, W. (2011). Transcranial direct current stimulation—Update 2011. *Restorative Neurology and Neuroscience, 29,* 463–492.

Okano, A. H., Fontes, E. B., Montenegro, R. A., Farinatti, P. D. T. V., Cyrino, E. S., Li, L. M., … Noakes, T. D.(2013). Brain stimulation modulates the autonomic nervous system, rating of perceived exertion and performance during maximal exercise. *British Journal of Sports Medicine*. doi:10.1136/bjsports-2012-091658

Pollok, B., Boysen, A. C., & Krause, V. (2015). The effect of transcranial alternating current stimulation (tACS) at alpha and beta frequency on motor learning. *Behavioural Brain Research, 293,* 234–240.

Reis, J., Schambra, H. M., Cohen, L. G., Buch, E. R., Fritsch, B., Zarahn, E., et al. (2009). Noninvasive cortical stimulation enhances motor skill acquisition over multiple days through an effect on consolidation. *Proceedings of the National Academy of Sciences, 106*(5), 1590–1595.

Ring, C., Cooke, A., Kavussanu, M., McIntyre, D., & Masters, R. (2015). Investigating the efficacy of neurofeedback training for expediting expertise and excellence in sport. *Psychology of Sport and Exercise, 16,* 118–127.

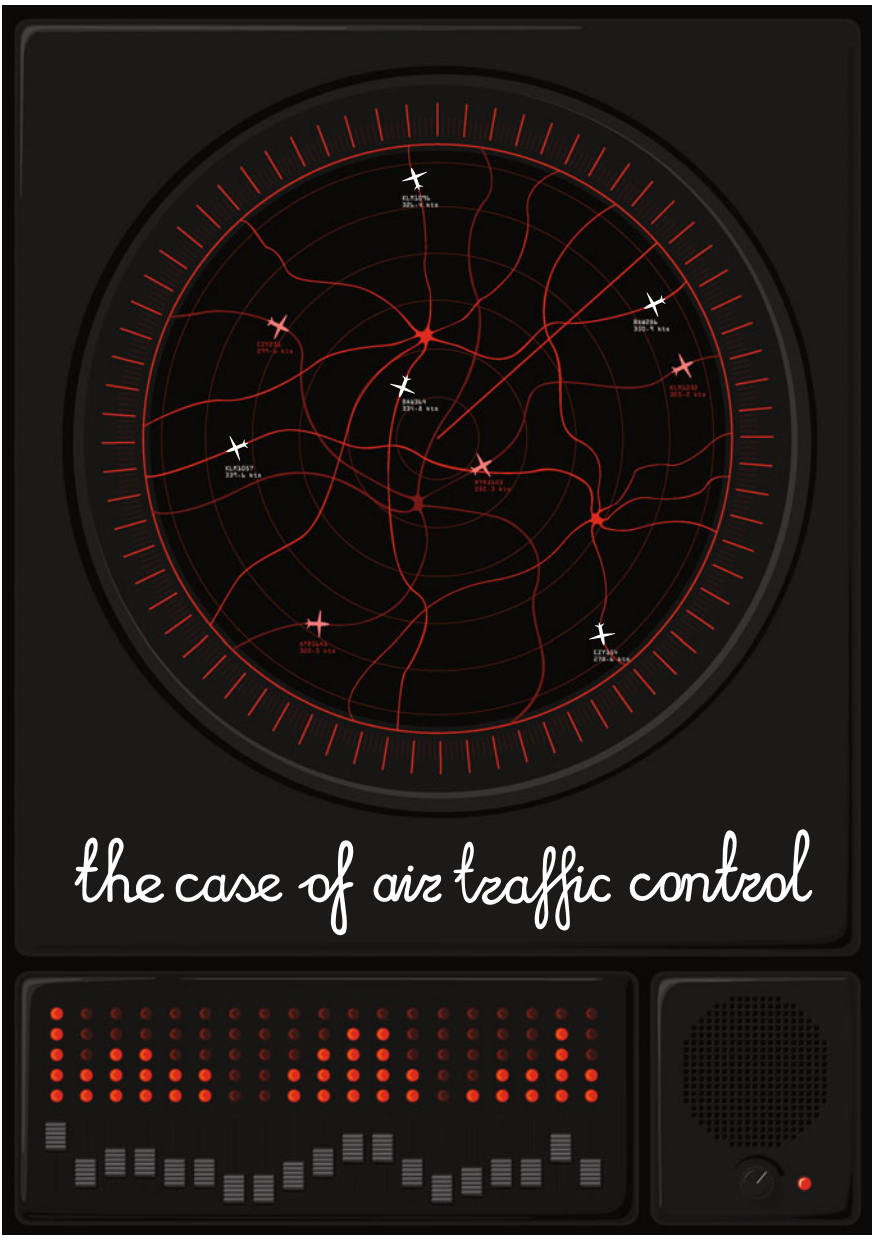
Rockstroh, B., Elbert, N., Birbaumer, N., & Lutzenberger, W. (1982). *Slow brain potentials and behavior*. Baltimore: Urban & Schwarzenberg.

Rostami, R., Sadeghi, H., Karami, K. A., Abadi, M. N., & Salamati, P. (2012). The effects of neurofeedback on the improvement of rifle shooters' performance. *Journal of Neurotherapy, 16*(4), 264–269.

Vitor-Costa, M., Okuno, N. M., Bortolotti, H., Bertollo, M., Boggio, P. S., Fregni, F., et al. (2015). Improving cycling performance: Transcranial direct current stimulation Increases time to exhaustion in cycling. *PLoS One, 10*(12), e0144916.

Williams, P. S., Hoffman, R. L., & Clark, B. C. (2013). Preliminary evidence that anodal transcranial direct current stimulation enhances time to task failure of a sustained submaximal contraction. *PLoS One, 8*(12), e81418.

Zhu, F. F., Yeung, A. Y., Poolton, J. M., Lee, T. M., Leung, G. K., & Masters, R. S. (2015). Cathodal transcranial direct current stimulation over left dorsolateral prefrontal cortex area promotes implicit motor learning in a golf putting task. *Brain Stimulation, 8*(4), 784–786.


the case of air traffic control

The Case of Air Traffic Control

Antonino Vallesi

Introduction

Air traffic controllers (ATC), especially radar controllers, have the important mission of guaranteeing the safety of highways in the sky, in the face of constantly increasing air traffic. The overall purpose of their job is indeed to ensure the smooth and efficient management of complex air traffic (Wickens et al. 1997). In particular, ATC predict future flight paths based on their perception and interpretation of multiple data on the radar display, such as speed, altitude, aircraft capability, and weather conditions, not only to preserve aircraft separation and avoid collisions, but also to efficiently minimize flying time and fuel costs. Additionally, they also have to constantly receive, send and negotiate instructions with other colleagues and pilots.

All these demands make ATC a special profession that requires intensive, life-long training and, as such, represents a very useful model of how life experiences may shape and boost cognitive functions. Despite this, as it will become clearer throughout this chapter, only a few systematic attempts have been made to characterize what becomes special in the cognitive architecture of ATC in comparison to other training programs and professional experiences.

The present chapter is organized in the following subsections. I will first describe the general cognitive profile that is supposed to explain the ATC profession. I will subsequently present some studies that try to elucidate what specific cognitive boosting is obtained with training and experience in ATC. Third, a few ergonomics

A. Vallesi (✉)
Department of Neuroscience, University of Padova,
via Giustiniani, 5, 35128 Padua, Italy
e-mail: antonino.vallesi@unipd.it

A. Vallesi
San Camillo Hospital IRCCS, Venice, Italy

L.S. Colzato, *Theory-Driven Approaches to Cognitive Enhancement*,
DOI 10.1007/978-3-319-57505-6_21

considerations in terms of man–technology interaction typical of ATC will be elucidated. Finally, some considerations on the methodological limits of the research conducted so far and proposals for future studies will precede the general conclusions.

General Cognitive Profile of ATC

Cognitive demands in ATC could be divided in at least four core processes: monitoring, controlling, checking, and diagnosing (Kallus et al. 1997). Monitoring consists of comparing the actual state of air traffic situation with the expected state, while controlling requires intervention, for instance by selecting a strategy, allocating time, or deciding to terminate an action. Obviously monitoring also intervenes to judge the outcome of controlling, thus the two processes are highly interrelated. Checking instead occurs less frequently in unexpected and potentially risky situations, when there is a misfit between the expected scenario and the current one. A psychological state of anxiety is usually associated with checking. Diagnosing consists of assimilating the new, unexpected traffic situation into the actual mental picture (with a consequent restored awareness of the current situation) or vice versa, often with the aid of a close inspection of the immediately past situation.

Monitoring and controlling are proactive processes driven by the mental model of the controller, whereas checking and diagnosing are driven by events. In particular, diagnosing is directed to reestablish a coherent mental picture and situational awareness, that is, the correspondence between the mental picture and the information about the environmental situation, allowing to switch from reactive activity to proactive control. If no stored solution for a conflict situation can be derived, ATC have to begin active decision-making or even problem-solving. Another important function in ATC is self-monitoring (Kallus et al. 1997): ATC have to continuously evaluate their internal state (e.g., fatigue), their own performance and their capacity of decision-making (e.g., risk-taking).

If one would like to precisely perform a formal cognitive task-analysis of the ATC job, more lab-based experimental studies should be carried out. This is not an easy task, since it is hard to capture the complex nature of the ATC cognitive challenges in a well-controlled lab setting. For instance, given the need to constantly monitor and control for critical events, one could envisage the ATC job mainly as a vigilance task. However, classical laboratory-based vigilance tasks (Parasuraman and Davies 1977) have an only apparent resemblance with the ATC job (Donald 2008). Differences can be seen at multiple levels. First, ATC situational awareness goes beyond the first perceptual level of lab tasks to also involve deeper levels such as interpretation of the current situation and prediction of upcoming scenarios. Other ATC-specific demands include the constant need to create 3-D mental pictures based on 2-D data, and the requirement to deal with multiple targets, that is, the various aircraft on a radar display and their interrelationships, in contrast with traditional vigilance research, where there is a single or only a few targets and many distracters (Wolfe et al. 2002). Finally, ATC work under a lot of

time pressure and with dynamically changing data. Their actions need to be as proactive as possible. This type of continuous change differs from classical vigilance tasks, which do not usually include the information-processing demands of continuously updated and time-critical situational awareness.

In addition to monitoring and planning, controllers have a lot of responsibilities, including liaising with other colleagues from other sectors, providing instructions, advice and information to pilots, dealing with requests and irregular events. Cognitive processes such as selective and divided attention, the use of mental models, scan patterns, interpretation and abstraction are crucial in the ATC job. In sum, the multitasking nature of their job makes the processes required in ATC fundamentally different from those traditionally studied in the lab.

Boosting Cognitive Functioning Through Training and Experience in ATC: Cognitive Benefits

Very few studies focused on the cognitive benefits of the initial ATC training, despite the fact that most changes should generally be expected during the early stages of learning, both at the behavioral (Anderson 2000; Thorndike 1898) and neural (Barnes 1979; Cooke and Bear 2010) levels.

One recent study (Arbula et al. 2016) tried to capture changes specific to ATC training in cognitive processing through a mixed longitudinal and cross-sectional design. ATC students were tested twice, a year apart, both at the beginning and at the end of their training with a battery including a task-switching paradigm. A control group consisting of age- and education-matched university students was also tested with a similar time schedule. The task-switching paradigm included two conditions with a short interval (100 ms) and a long one (1000 ms) between the instructional cue and the target (CTI). When the cue is presented much earlier than the target, preparation for the next task is possible and a proactive type of control adjustment is more likely to be engaged; conversely, when the CTI is short, there is not enough time to prepare for the task and its implementation relies more on a post-target reactive type of control (Ruge et al. 2003).

It is possible to hypothesize an advantage of ATC in both reactive and proactive control given that, as already stated in the previous section, they have to monitor and control the current scenario (proactive control) but also check and diagnose unusual situations (reactive control). Arbula et al. (2016) showed that reactive control [measured through the response time (RT) cost of switching rules with short CTI] is enhanced after ATC training. Conversely, the proactive control involved in the selection and maintenance of task relevant information, which was measured with the RT cost when a rule is repeated in mixing blocks versus single task ones with long CTI, was already superior in the ATC students as compared with controls at baseline. It is probably necessary to boost reactive control early on in the ATC training to compensate for a lack of experience (e.g., a large repertoire of possible

scenarios, actions, and strategies) that would allow predicting the evolving air traffic situation well in advance.

To obtain a more complete picture, it would also be useful to understand the role of experience in shaping the cognitive mechanisms in professional ATC. Amaldi (1994) performed qualitative naturalistic observations and interviews on 13 controllers with different levels of expertise, which allowed drawing some tentative conclusions. Experience controllers had: a larger repertoire of traffic patterns and relationships between traffic scenarios; stronger and advanced planning actions; higher capacity to keep multiple plans and alternatives active in parallel under complex traffic situations. As a consequence, less experience means higher overload, anxiety, and stress, because of a failure to monitor expected developments of current traffic scenarios and of a more reactive attitude compatible with the results by Arbula et al. (2016).

Thus, experience means more knowledge and more capacity to use knowledge, time, and cognitive resources to come up with effective plans. Generally, experienced decision-makers use less information (Shanteau 1992), but this information is more relevant to the task at hand. According to training studies (e.g., Haider and Frensch 1996), performance improvements derive from increasing distinction between more and less relevant information. This issue has been also investigated in ATC.

In particular, in a study by Malakis and Kontogiannis (2013) expert and novice ATC were compared in their job contexts. Despite the limited sample size ($N = 10$), a qualitative analysis, mainly based on statements by on-the-job training instructors, suggested that experts were more able to hold most of the relevant information for difficult scenarios than novices. They were also more sensitive to the operational contexts and receptive to flight crew preferences even in complex scenarios, and used a larger repertoire of strategies to come up with well-crafted solutions. Novices decreased their performance especially with very demanding scenarios (also see Amaldi 1994), in which they were so focused on minimizing conflicts and organizing the traffic that it was difficult to take into consideration all possible factors. For instance, novices often neglected weather conditions and their evolution, terrain features and crew's preferences. In other words, they were engaged in tighter and more fragile planning than experts. When novices were able to take into account deteriorating weather by building new cognitive maps to adjust route deviations, they had to change their original overall traffic plan, with a consequence of causing delays and extensions to aircraft routes. Experts were more able to change plans and flexibly create a new setting when forced to do so (e.g., when the crew declared an emergency) in a less effortful manner (e.g., minimizing the need for constant monitoring). Experts may rely more on accumulated experience, for instance to deal with ghost tracks, or to disentangle whether a given depiction on the radar represents some weather phenomena (accumulated weather-related experience) or elevated terrain.

Cognitive benefits, at least in terms of ATC context-specific processes, could potentially be "transferred" from expert to novices by exposure. In a work by Kang and Landry (2014), for instance, short training periods in which expert scan-paths

were presented to novices reduced the number of false alarms in detecting loss of separation in the latter group, although not the detection of loss of separation per se. This result is still important given that false alarms elicit maneuvers that produce a fuel burn penalty, impact on schedule, and unneeded effort in determining and executing problem resolutions.

Nonetheless, evidence of experience-dependent advantages in ATC is not always compelling. In a study adopting an experimental approach (Niessen et al. 1999), 35 controllers with three different levels of experience were recruited (experiment 1). They were required to control a familiar realistic scenario lasting for 20 min. To investigate the selection of information, features of aircraft on the radar screen and the flight-strip system were masked with gray bars. The signs could be unmasked by moving the pointer of the computer mouse to the respective location. The controller's task was to control the familiar traffic safely and effectively. The degree of experience revealed no significant differences. There was a general preference for using long-term rather than short-term planning data, an information selection strategy that seems to be acquired already during the first years of professional practice. However, the strategies of data selection may continue to change over many years, since some of the data showed a marginal reduction in the selection of planning data. In a second experiment, ATC had to sort the situations according to subjective similarity. Again, no experience-dependent difference emerged, since both groups produced about identical solutions that showed classification criteria based on the amount of monitoring and anticipation subjectively needed.

Some studies focused on possible benefits of ATC in aging. Since an important by-product of age is experience, this could help solve complex problems by compensating for possible age-related cognitive deficits. This may be also true for ATC. A study (Nunes and Kramer 2009) recruited older (53–64 years old) and younger (25–38 years old) professional ATC and two groups of age-matched controls. The battery of tests used included both domain relevant abilities (inhibition, task-switching, visuospatial ability, working memory, breadth of attention), and less relevant ones (inductive reasoning and processing speed). Moreover, ATC tasks were also administered to assess problem-solving under different levels of time pressure in various ATC scenarios. The results showed experience-based sparing on two domain-relevant abilities, that is, inhibition, as studied with a Flankers task, and visuospatial ability, as studied with a mental rotation task. Other abilities did not show experience by age interaction. Particularly surprising was the null result with task-switching. Probably switching becomes more automatic and processes are so integrated after many years of experience that switching abilities are not required any more. Also unexpected was the lack of an experience by age interaction in working memory. Probably experienced ATC rely more on external aids (e.g., radar, flight progress strips) to maintain situational awareness than on internal working memory, which has a limited capacity, and becomes even more reduced with advancing age (Hedden and Gabrieli 2004). Finally, concerning breadth of attention, it is possible that ATC serially focus attention on specific aircraft rather than processing multiple aircraft in parallel (see also Kang et al.

2014). The authors concluded that experience does not provide immunity against the detrimental effects of age on every function but on the most domain-relevant ones only.

Similar results were obtained with simulated ATC tasks (Nunes and Kramer 2009), where performance of older and younger ATC was similar especially in more difficult problem-solving tasks. There was also no difference in aircraft handling capacity and airspace management. In fact, sometimes, younger ATC issued more commands than necessary compared with older ATC, which demonstrated that older ATC adopt a more efficient, possibly compensatory strategy of issuing fewer commands while achieving the same results. Probably seasoned older professionals use alternative strategies that exploit a domain-relevant acquired repertoire of information to efficiently manage complex sociotechnical systems (also see Bäckman and Dixon 1992).

However, it should be noted that years spent in ATC not only increase experience but also the risk of burnout. Burnout is a state of emotional, mental, and physical exhaustion caused by excessive and protracted stress. Since burnout is related to changes in mood and behavior, it may therefore become safety relevant. The risk of burnout increases with age in ATC especially in interaction with low social support, work stressors and professional dissatisfaction (Dell'Erba et al. 1994).

Ergonomics and Man–Technology Interaction in ATC

The man–technology interaction necessary in ATC (especially with radar displays and communication tools) clearly represents both an opportunity to make the job environment more ergonomic and a cognitive challenge. Many steps could go wrong and cause different kinds of problems, involving several cognitive components.

Some of these issues are actively faced by ATC. For instance, to effectively use limited cognitive resources, active professional ATC report that they develop visual strategies (e.g., circular, linear, zooming out, regional) as heuristics to efficiently search for possible conflicts, minimizing the need of effortful scanning of each aircraft pair (Kang et al. 2014). Other issues probably need to be solved by more preemptive ergonomic changes in the environment. Once the cognitive vulnerabilities of the human information-processing system are well characterized, it is indeed possible to modify the environmental design and system factors in ways that may minimize these vulnerabilities (Wickens et al. 1997).

For instance, redundancy and error tolerance in the system could help working memory and reduce mistakes (Burke-Cohen 1995). Moreover, increased consistency of operating rules and procedures would attenuate negative transfer and slips in long-term memory, such as when operators need to be relocated at a different site. Finally, reduction of information load and distracting information would aid visual sampling and selective attention (Wickens and Carswell 1995), while cueing

salient information through technological aids may increase situation awareness (Sarter and Woods 1995).

Final consideration concerns the degree of automation in ATC, which constantly increases with the goal of improving safety and efficiency and thanks to technological advancements (The Future of Air Traffic Control 1998). The effects of automation are controversial, with some reports finding enhanced prospective memory and planning, possibly due to the reduced working memory load (Vortac et al. 1993), other reports highlighting extra effort, for instance, due to the need to compensate for system deficiencies and to reorganize problem-solving or cooperation strategies (e.g. Amaldi et al. 2000), and yet others suggesting clearly detrimental effects (e.g., Metzger and Parasuraman 2001).

Methodological Issues in the Research on the Cognitive Benefits of ATC

As previous paragraphs clearly showed, the research on the cognitive enhancement derived from training and experience on ATC is scant and in need of methodological improvements. In general, very few studies were well controlled, probably because the aim of most investigations was more exploratory and descriptive. Most studies conducted so far adopted a qualitative approach, including naturalistic observations, or interviews to ATC or to their training instructors. Many works did not include control participants such as non-ATC with comparable demographic characteristics and comparable training or professional history. The sample size was often very small (usually ranging from 5–6 to less than 20) and, what is worse, some studies inappropriately used parametric statistics (e.g. *t*-test) for these very small samples. Finally, in various studies the researchers tested just one expertise level or there was no focus on this factor.

Future investigation would clearly benefit from the use of portable neuroimaging tools, as already indicated in some recent ergonomic studies. For instance, Ayaz et al. (2012), tested six experienced controllers with functional near-infrared spectroscopy (which indirectly measures brain activity by tracking cortical oxygen consumption) over medial frontopolar cortex. ATC were administered different realistic air traffic situations varying in the degree of difficulty, which was operationalized as the number of aircraft that the controllers had to monitor and control, and as electronic versus voice communications. Increased task-difficulty was associated with monotonic increases of oxy-hemoglobin levels, paralleling the subjective workload judgments. These results suggest that activation in this brain region provides a valid measure of mental workload in this ATC task. An Event-Related Potential study (Giraudet et al. 2015) demonstrated how ATC requires sharing attentional resources among different modalities (visual, auditory). In particular, the authors found an increased auditory P300 to rare pitch tones with an easier-to-process visual notification design. This finding demonstrates that the amount of resources used for processing one modality is inversely related to that

used for processing the other. Further studies with these portable neuroimaging techniques are required to shed light on how neurocognitive processes specifically change with ATC experience.

Conclusions

The few studies that have investigated the role of training and experience in air traffic control suggest that this profession shapes various aspects of cognitive flexibility, including enhanced reactive control with early training and better proactive planning with years of professional experience. Finally, some unique cognitive challenges are represented by man–technology interactions inherent to this job. Despite the emerging evidence reviewed in this chapter, the research on the cognitive enhancement derived from training and experience on ATC is still scant and further methodologically well-controlled studies are needed.

Acknowledgements AV is funded by the European Research Council (ERC) starting Grant LEX-MEA (GA# 313692).

References

Amaldi, P. (1994). RADAR controller's problem-solving and decision-making skills. In J. A. Wise et al. (Eds.), *Verification and validation of complex systems: Additional human factors issues*. USA: Embry-Riddle Aeronautical University.

Amaldi, P., Barale, G., & Di Rienzo, N. (2000). *Putting in operation a complex system is not only a technical challenge*. Paper presented at the third USA/Europe Air Traffic Management Seminar. Available at http://atm-seminar-2000.eurocontrol.fr/

Anderson, J. R. (2000). *Learning and memory: An integrated approach* (2nd ed.). New York: Wiley.

Arbula, S., Capizzi, M., Lombardo, N., & Vallesi, A. (2016). How air traffic control training shapes cognitive control strategies: The case of air traffic control training. *PLoS ONE, 11*(6), e0157731. doi:10.1371/journal.pone.0157731

Ayaz, H., Shewokis, P. A., Bunce, S., Izzetoglu, K., Willems, B., & Onaral, B. (2012). Optical brain monitoring for operator training and mental workload assessment. *NeuroImage, 59*(1), 36–47. doi:10.1016/j.neuroimage.2011.06.023

Bäckman, L., & Dixon, R. A. (1992). Psychological compensation: a theoretical framework. *Psychological Bulletin, 112*(2), 259–283.

Barnes, C. A. (1979). Memory deficits associated with senescence: A neurophysiological and behavioral study in the rat. *Journal of Comparative and Physiological Psychology, 93*(1), 74–104.

Burke-Cohen, J. (1995). Traffic control clearances. In B. G. Knaki & O. V. Prinzo (Eds.), *How to say it and how much: The effect of format and complexity on pilot recall of air traffic control clearances, Prepared for Office of Aviation Medicine, Federal Aviation Administration* (pp. 29–38). Washington: US Department of Transportation.

Cooke, S. F., & Bear, M. F. (2010). Visual experience induces long-term potentiation in the primary visual cortex. *Journal of Neuroscience, 30*(48), 16304–16313. doi:10.1523/JNEUROSCI.4333-10.2010

Dell'Erba, G., Venturi, P., Rizzo, F., Porcù, S., & Pancheri, P. (1994). Burnout and health status in Italian air traffic controllers. *Aviation, Space, and Environmental Medicine, 65*(4), 315–322.

Donald, F. M. (2008). The classification of vigilance tasks in the real world. *Ergonomics, 51*(11), 1643–1655. doi:10.1080/00140130802327219

Wickens, C. D., Mavor, A. S., & McGee, J. P. (Eds.). (1997). *Flight to the future: Human factors in air traffic control*. Washington: National Academies Press.

Giraudet, L., Imbert, J.-P., Bérenger, M., Tremblay, S., & Causse, M. (2015). The neuroergonomic evaluation of human machine interface design in air traffic control using behavioral and EGG/ERP measures. *Behavioural Brain Research, 294,* 246–253. doi:10.1016/j.bbr.2015.07.041

Haider, H., & Frensch, P. A. (1996). The role of information reduction in skill acquisition. *Cognitive Psychology, 30*(3), 304–337.

Hedden, T., & Gabrieli, J. D. E. (2004). Insights into the ageing mind: a view from cognitive neuroscience. *Nature Reviews Neuroscience, 5*(2), 87–96. doi:10.1038/nrn1323

Kallus, K. W., Barbarino, M., & Van Damme, D. (1997). *Model of the cognitive aspects of air traffic control*. Belgium: European Organisation for the Safety of Air Navigation.

Kang, Z., Bass, E. J., & Lee, D. W. (2014). Air traffic controllers' visual scanning, aircraft selection, and comparison strategies in support of conflict detection. In *Proceedings of the 58th Annual Meeting of the Human Factors and Ergonomics Society. Chicago, IL* (Vol. 68(1), pp. 77–81).

Kang, Z., & Landry, S. J. (2014). Using scanpaths as a learning method for a conflict detection task of multiple target tracking. *Human Factors, 56*(6), 1150–1162.

Malakis, S., & Kontogiannis, T. (2013). A sensemaking perspective on framing the mental picture of air traffic controllers. *Applied Ergonomics, 44*(2), 327–339. doi:10.1016/j.apergo.2012.09.003

Metzger, U., & Parasuraman, R. (2001). The role of the air traffic controller in future air traffic management: An empirical study of active control versus passive monitoring. *Human Factors, 43*(4), 519–528.

Niessen, C., Eyferth, K., & Bierwagen, T. (1999). Modelling cognitive processes of experienced air traffic controllers. *Ergonomics, 42*(11), 1507–1520. doi:10.1080/001401399184857

Nunes, A., & Kramer, A. F. (2009). Experience-based mitigation of age-related performance declines: Evidence from air traffic control. *Journal of Experimental Psychology Applied, 15*(1), 12–24. doi:10.1037/a0014947

Parasuraman, R., & Davies, D. R. (1977). A taxonomic analysis of vigilance. In R. R. Mackie (Ed.), *Vigilance: Theory, operational performance, and physiological correlates* (pp. 559–574). New York: Plenum.

Ruge, H., Brass, M., Lohmann, G., & von Cramon, D. Y. (2003). Event-related analysis for event types of fixed order and restricted spacing by temporal quantification of trial-averaged fMRI time courses. *Journal of Magnetic Resonance Imaging, 18*(5), 599–607. doi:10.1002/jmri.10397

Sarter, N. B., & Woods, D. D. (1995). How in the world did we ever get into that mode? Mode error and awareness in supervisory control. *Human Factors, 37*(1), 5–19. doi:10.1518/001872095779049516

Shanteau, J. (1992). How much information does an expert use? Is it relevant. *Acta Psychologica, 81*(1), 75–86. doi:10.1016/0001-6918(92)90012-3

The Future of Air Traffic Control. (1998). *Human operators and automation*. Washington: National Academies Press. Retrieved from http://www.nap.edu/catalog/6018

Thorndike, E. (1898). Some experiments on animal intelligence. *Science, 7*(181), 818–824. doi:10.1126/science.7.181.818

Vortac, O. U., Edwards, M. B., Fuller, D. K., & Manning, C. A. (1993). Automation and cognition in air traffic control: An empirical investigation. *Applied Cognitive Psychology, 7*(7), 631–651. doi:10.1002/acp.2350070707

Wickens, C. D., & Carswell, C. M. (1995). The proximity compatibility principle: Its psychological foundation and relevance to display design. *Human Factors, 37*(3), 473–494. doi:10.1518/001872095779049408

Wolfe, J. M., Oliva, A., Horowitz, T. S., Butcher, S. J., & Bompas, A. (2002). Segmentation of objects from backgrounds in visual search tasks. *Vision Research, 42*(28), 2985–3004.

the case of the leiden "lifestyle 2030" study

www.deleidseproeftuin.nl

The Case of the Leiden "Lifestyle 2030" Study

Kerwin J.F. Olfers, Guido P.H. Band, Lorenza S. Colzato and Bernhard Hommel

Introduction

In 2003, 92-year-old Fauju Singh set the marathon world record for 90+ year olds (BBC News 2005), finishing in less than 6 hours; an impressive example of physical prowess at older age. Unfortunately, the reality is that the majority of older adults will experience some form of age-related health decline (World Health Organization 2011), which is of particular relevance as most Western societies are ageing rapidly (UNFPA and HelpAge 2012). As a result, older adults receive less financial support, have limited access to care-homes and in-home care, and are thus required to live independently for longer. These developments create the urgent need to promote self-reliance and quality of life in older age—vitality, as we will call it (following Westendorp 2015), regardless of changes in health.

Several promising avenues towards enhancing successful ageing by means of cognitive interventions have been identified in the literature (Lustig et al. 2009). However, less is known about how well such interventions translate into real-world application. For instance, are the interventions easily accessible to the ageing population at large, and do they retain their efficacy when implemented outside of the lab setting? To address these issues we conducted a large-scale cognitive enhancement study at Leiden University: *Lifestyle 2030*, to which all Leiden citizens above 55 years of age were invited and for which interventions were implemented that were thought to be easy to access by all participants through the internet. In this chapter,

K.J.F. Olfers · G.P.H. Band · L.S. Colzato (✉) · B. Hommel
Cognitive Psychology Unit and Leiden Institute for Brain and Cognition, Leiden University, Leiden, The Netherlands
e-mail: colzato@fsw.leidenuniv.nl

L.S. Colzato
Institute of Cognitive Neuroscience, Faculty of Psychology, Ruhr University Bochum, Bochum, Germany

L.S. Colzato, *Theory-Driven Approaches to Cognitive Enhancement*,
DOI 10.1007/978-3-319-57505-6_22

we will use *Lifestyle 2030* to illustrate both theoretical considerations and practical challenges in designing and running such a project. First, we will discuss the types of cognitive enhancement interventions that might improve self-reliance and independence in the ageing population. Then, we will consider how successful *Lifestyle 2030* was in guaranteeing ecological and population validity. We will argue that an online approach to intervention studies offers unique benefits for both kinds of validity but also brings with it some important drawbacks that warrant further attention.

Lifestyle 2030 Interventions

The notion that physical health does not directly translate into independence and perceived quality of life has been demonstrated in interventions such as the Successful Ageing Evaluation study (Jeste et al. 2014). Everyday functioning and mental well-being in old age depend on cognitive functioning, and both are hampered by age-related decline in cognitive control (Hertzog et al. 2009; Schaie 1994), mild cognitive impairments (Allaire et al. 2009; Burton et al. 2009), and even by personal concerns about cognitive decline (Smith et al. 2009). Together, these findings indicate the need to slow down or even reverse cognitive decay in the ageing population, as cognitive vitality is key in meeting the growing demands for self-management, self-reliance and successful ageing.

Although age-related decline in cognitive functioning is a thoroughly established phenomenon (Salthouse 2009), there is substantial inter-individual variability. Various lifestyle factors have been identified as possible moderators of this variability. In particular, lifestyles that can be characterized as active and which may include lifelong learning, mental and physical exercise, proper nutrition, and social engagement, are positively associated with cognitive vitality (Fillit et al. 2002; Hertzog et al. 2009).

Leveraging such moderators and the principles of brain plasticity, a substantial body of research has shown positive effects of different intervention types on cognitive performance in elderly. Promising interventions including physical exercise (Bherer et al. 2006; Voss et al. 2011; see also Chapter "Aerobic Exercise"), cognitive training (Buschkuehl et al. 2008; Karbach and Kray 2009), music (Alain et al. 2014; Bidelman and Alain 2015; see also Chapter "Musical Activities and Cognitive Enhancement in Dementia"), video game training (Anguera et al. 2013; Basak et al. 2008), bilingualism (Bialystok et al. 2012) and meditation (Gard et al. 2014). Using various neuroimaging techniques, such interventions have also been linked to corresponding physical changes in the brain (Erickson et al. 2009; Lustig et al. 2009).

While these studies show encouraging results, comparisons of intervention types across studies are often difficult due to differences in sample selection, intervention methodology, and tested measures. A positive trend in recent studies is to compare multiple types of interventions directly, thereby at least partially circumventing such issues. For example, Gajewski and colleagues (2012) compared the effects of cognitive, physical, and relaxation training against performance of a no-contact control group, in 140 healthy participants of 65 years and older. After 4 months of

semi-weekly 90-min training sessions, the cognitive training group showed greater improvements than the other groups on measures of cognitive flexibility, working memory, and associated brain potentials.

In *Lifestyle 2030,* we expanded on this approach, by randomly assigning participants to one of the six promising intervention types: physical exercise, focused or open meditation, learning a new language (Russian or Chinese), and brain training games, or to an active control condition (watching TV-shows). Pre and post-test measures included extensive online questionnaires assessing demographics, lifestyle, and subjective well-being. Additionally, we used four well-established cognitive tasks to assess attention (field of view task; Ball et al. 2007), working memory (N-back task; Kirchner 1958), inhibition (Simon Task; Hommel 1993), and cognitive flexibility (Task Switch paradigm; Karayanidis et al. 2003). In sum, the interventions and test measures were chosen to allow for meaningful comparisons of intervention effects, both within the study and with regard to other studies.

Ecological Validity Through Online Interventions

The entire *Lifestyle 2030* study, including all interventions, instructions and data collection, was implemented on an online platform, to maximize ecological validity. Ecological validity refers to how closely the testing environment matches the intended real-world environment, which is an excellent predictor of how generalizable observed effects are (Bracht and Glass 1968; Schmuckler 2001). For cognitive enhancement interventions this definition should be expanded to include not just the testing environment, but the training environment as well. This aspect of ecological validity is increasingly important, as the driving force behind enhancement studies for the ageing population is not so much the fundamental question whether cognitive performance can be improved in principle but the more practical question whether successful interventions can be implemented in an effective and accessible way. In the following, we will discuss three key issues one is often facing when trying to maximize ecological validity.

Costs and Access

Some interventions might be more suited than others for actual large-scale implementations that target the ageing population as a whole, simply due to practical reasons. For instance, while a highly supervised physical exercise training (Colcombe et al. 2004) might yield stronger results than a computerized brain training game (Owen et al. 2010), the costs involved in intervention programs that require constant guidance or labour-intensive monitoring become prohibitively large as the size of the target audience increases. Moreover, some interventions might not be accessible to older adults due to location, limited mobility, or insufficient financial resources to purchase expensive hardware such as gaming consoles.

For *Lifestyle 2030*, all a participant needed was access to a pc, laptop, or tablet with an internet connection and an up-to-date browser. Furthermore, many tasks such as data collection, screening, reminders and so forth were largely automated, implying very low-maintenance and minimal experimenter supervision. This online browser-based format has the distinct advantages of low running cost and high accessibility for all interventions, essentially levelling the playing field in terms of applicability outside the scope of research.

As an example, in the physical exercise condition, participants were not asked to follow a specific exercise routine or join a sports group. Instead participants reported on their physical activities on a daily basis, by indicating the type and duration of the activities engaged in since the previous report. The participants would then be shown the amount of calories expended during these activities and encouraged to incrementally improve on this number for the next session. Suggestions for increasing daily physical activity included longer or more frequent repetitions of previous activities (e.g., walking, riding a bike or swimming), or taking up new activities (e.g., playing golf). In short, this setup allowed for participation regardless of current physical fitness or access to sports facilities.

Lab-Based Versus at-Home Efficacy

Even interventions that in theory do not require any hands-on approach might still yield different results when administered in the lab rather than in a real-world at-home setting. Cognitive enhancement studies that use commercially available online brain training software seem promising candidates for strong ecological validity, as these interventions are already highly accessible and are voluntarily being used by millions of people (Sternberg et al. 2013). One study administered at-home online brain training games to older adults with mild cognitive impairments (MCI), and found tentative evidence for improved visual sustained attention after 30 sessions, when compared to a waitlist control group (Finn and McDonald 2011).

However, beneficial effects of computerized cognitive training (CCT) for trained and untrained cognitive functions have mostly been reported in lab-based studies (Ballesteros et al. 2015). Some studies failed to find any effects of CCT in at-home settings at all. For instance, in a collaboration with the BBC involving over 11,000 participants, Owen et al. (2010) found no significant cognitive improvements after participants followed one of two separate CCT interventions at home, as compared to an active control condition.

The inclusion of active and no-contact control groups ensures that effects are not solely due to social interactions with experimenters—conditions that induce Hawthorne or social facilitation-like effects (Zajonc 1965). However, such controls unfortunately cannot rule out that these social factors are necessary components for the training to be effective. In fact, a review of 52 computerized cognitive training studies suggests unsupervised at-home training to be generally ineffective, in contrast to supervised in-lab training (Lampit et al. 2014).

Others have pointed out that factors that might undermine intervention efficacy for at-home studies include: differences in expectation, motivation and enjoyment, low intensity or diversity in training, low training adherence and high drop-out rates (Boot et al. 2011; Buitenweg et al. 2012; Lampit et al. 2014). Conversely, providing interventions at-home seems better suited to encourage context-dependent learning and habit-forming behaviour than lab-based interventions, potentially sustaining beneficial effects on the long-term. It is precisely in such factors that discrepancies between lab-based studies and real-world implementations might be expressed, limiting the ecological validity of reported effects.

Design and Dropout

The above observations highlight one of the major difficulties in designing interventions: finding the appropriate balance between enough sessions to realistically yield meaningful results, while not making the intervention so long or intense that training compliance and completion drop too severely. In a meta-analysis of training effect modifiers, Lampit and colleagues (2014) found that sessions shorter than 30 min might be too short to produce results, and suggested 30–60 min sessions better target synaptic plasticity. Furthermore, providing more than three sessions per week also seemed to undermine training effectiveness, possibly inducing cognitive fatigue. Moving from a lab setting to the real world, this balance might be expected to shift even further, as diminished interaction with experimenters will lead to decreased adherence and even lower tolerance for required effort.

In fact, this was the main problem we encountered in *Lifestyle 2030*, as drop-out rates over 40% were seen for interventions in a first phase of the study, consisting of 20 sessions, each lasting 45 min, over the course of eight weeks. Moreover, drop-out was negligibly reduced when the interventions were shortened to nine 45 min sessions over the course of four weeks in a second phase of the study. This problem seems to mirror the generally reduced effectivity of at-home as compared to lab or group-based interventions (Lampit et al. 2014). A potential remedy is to include more social factors, as these might support healthy ageing and cognition (Ballesteros et al. 2015). In the future, we could therefore explore options such as inter-participant contact via chat, social media or even competition elements.

In sum, a stronger focus on ecological validity seems warranted, specifically regarding the need for low-cost and easily accessible intervention programs that translate readily to real-world use. In *Lifestyle 2030* we attempted to tackle this issue by providing at-home interventions on the Internet, although problems with training adherence and dropout need to be addressed. An additional advantage of online intervention, as will be discussed in the next section, is the possibility for testing much greater and varied samples than lab-based testing would allow.

Population Validity Through Inclusive Design

Providing accessible and low-cost online intervention programs like *Lifestyle 2030* allows for a large and diverse participant sample, which promotes population validity. Population validity refers to the degree to which the tested sample is representative of the (target) population as a whole, and thereby allows for generalization of the results (Bracht and Glass 1968). Selecting representative samples is especially important for cognitive enhancement research aimed at older adults, as such samples constitute a sufficiently heterogeneous group with significant differences in age-related cognitive decline, physical and mental health, and overall living conditions (Breteler et al. 1994; Hedden and Gabrieli 2004). To illustrate, Yaffe and colleagues (2009) performed an 8-year longitudinal study of factors predicting maintenance of cognitive function in older adults, and identified three distinct groups of participants: cognitive maintainers (30%), minor cognitive decliners (53%) and major decliners (16%). These groups were also associated with differences in lifestyle factors including physical exercise, smoking behaviour, and social interaction. Population validity therefore is needed not just to answer the question which intervention is most effective, but more importantly, which intervention is most effective for whom.

Sample Selection

Accounting for differences in the ageing population is important to allow for meaningful comparisons across enhancement interventions and studies. While highly homogeneous samples (e.g., only male adults with MCI in care homes) might limit the generalizability of findings to the wider population, high heterogeneity within relatively small samples might instead obscure improvements related to the interventions. Thus, even when comparing highly similar studies it can become difficult to assess whether contrasting effects are rooted in design choices or in sample selection, let alone when comparing studies featuring different intervention types. For instance, while beneficial effects of combined CCT and physical exercise (CCT-P) over CCT-only were found in one study (Theill et al. 2013), a very similar study failed to find added benefit of physical exercise (Rahe et al. 2015). While specific implementations of the CCT-P might have caused these discrepancies, they could also be due to differences in sample characteristics between the studies, perhaps even through particular inclusion criteria. As an illustration, a third study found cognitive improvement after CCP-T in a group of 322 older adults as compared to a passive control, but both the strength and dose-dependence of the effects seemed linked to the presence and severity of neurocognitive disorders (Bamidis et al. 2015).

As mentioned in the previous section, the online and easy-access nature of the *Lifestyle 2030* interventions can be expected to lower the threshold for participation and allow a greater variety of participants. The low-cost aspect of online studies

also makes them ideally suited for scaling to larger groups, allowing for meaningful investigations of heterogeneous samples. Furthermore, both access to internet and active use of a computer are more prevalent in the ageing population than is often assumed. In 2013, daily internet users in the Netherlands included 80% of 55–65-year olds, and 70% of 65–75-year olds (Central Bureau for Statistics 2014).

However, digital naivety might still lead to self-selection, as another important reason for the previously mentioned dropout in *Lifestyle 2030* was the reported difficulties with the online platform, specifically during the pre and post-test phase. Although increasingly many software packages provide tools for online reaction time experiments (Barnhoorn et al. 2014; Inquisit 2014; Schubert et al. 2013), choosing the right software depends strongly on the use-case. For instance, while browser-based tasks are more accessible than external clients, they also increase the chance for older adults to accidentally exit the task, click the back button in the browser, or get distracted by other programs. Thus, extensive usability testing is required (Nielsen 1994), which goes well beyond standard piloting sessions. We experienced this first hand as our original task designs, based on many years of in-lab testing, proved virtually unusable for a test panel of older adults when they were asked to perform the tasks without experimenter guidance. These problems again might be partly mediated by incorporating stronger social aspects into the study, potentially by administering the pre and post-test measures in the lab, while keeping the interventions themselves online.

Individual Differences

Second, in recent years researchers have increasingly argued that individual differences might play a key role in cognitive enhancement studies, e.g., moderating participants' reactions to interventions and possibly enhancing, diluting or even neutralizing group wise averaged effects (Buitenweg et al. 2012; Hertzog et al. 2009). To illustrate, a logical expectation might be that a physical exercise intervention will boost cognitive performance most in people who are normally less physically active, also known as a compensation effect. Conversely, providing training interventions might actually produce the largest effects in people whose cognitive performance is already above average, also known as a magnification effect. Especially mnemonic training seems to improve memory performance more for those who already scored higher before training (Lövdén et al. 2012).

In *Lifestyle 2030,* we therefore recorded a wealth of potentially relevant background data using several well-known, validated questionnaires, supplemented with our own custom items. Information of interest included the usual demographic and socioeconomic factors, information about current and past health (e.g., diseases or strokes), lifestyle indicators relating to media use (Ellison et al. 2007), religion, well-being (Brown and Ryan 2003), sleep quality (Buysse et al. 1989), physical exercise (Craig et al. 2003), life-events that we know are predictors for subsequent vulnerability (such as the passing of close relatives), and finally certain criterion behaviours associated with vitality and self-reliance (Broadbent et al. 1982).

We hope that in the future this information will even allow us to design and provide tailored interventions targeted to the specific needs and characteristics of each individual, as greater improvements of cognitive functions are likely to be expected with a more personalized approach (Peretz et al. 2011; Whitlock et al. 2012).

Finally, training efficacy might be influenced not just by overt behavioural differences but also much more subtle differences including neurotransmitter-related genotypes. In a game-based cognitive training study with elderly people, participants with a genetic predisposition to higher levels of activity-dependent secretion of brain-derived neurotrophic factor (BDNF), showed stronger transfer effects to attentional processes, than those without the particular genotype (Colzato et al. 2011). In this sense, purely online approaches seem to offer little direct advantage and would at least require additional genetic and physiological measures. However, mixed online and in-lab studies would allow for large sample sizes, which are essential given the often unequal distribution of genotypes in the population.

Conclusion

To conclude, we have argued that a greater demand for self-reliance and independent living at older age calls for the development of effective enhancement interventions that promote cognitive vitality. Importantly, to allow for application in real-world scenarios, these interventions should be easily accessible to the ageing population at large, retain their efficacy when implemented outside of the lab setting and allow for tailored assignment to relevant individual differences. Using the *Lifestyle 2030* study we illustrated how an online intervention approach can address these issues of ecological and population validity, by providing a wide range of easy-access at-home interventions, allowing for large inclusive samples, and recording a wealth of background information. However, there is no one-size-fits-all approach, and our experience with *Lifestyle 2030* indicates several challenges that still need to be addressed. Most notably online approaches seem susceptible to exacerbated problems of dropout, and yield reduced intervention efficacy. To this end, we suggest future studies could benefit from a stronger emphasis on social factors, and the inclusion of genetic and physiological measures.

References

Alain, C., Zendel, B. R., Hutka, S., & Bidelman, G. M. (2014). Turning down the noise: The benefit of musical training on the aging auditory brain. *Hearing Research, 308,* 162–173. doi:10.1016/j.heares.2013.06.008

Allaire, J. C., Gamaldo, A., Ayotte, B. J., Sims, R., & Whitfield, K. (2009). Mild cognitive impairment and objective instrumental everyday functioning: The everyday cognition battery memory test. *Journal of the American Geriatrics Society, 57*(1), 120–125. doi:10.1111/j.1532-5415.2008.02054.x

Anguera, J. A., Boccanfuso, J., Rintoul, J. L., Al-Hashimi, O., Faraji, F., Janowich, J., et al. (2013). Video game training enhances cognitive control in older adults. *Nature, 501*(7465), 97–101. doi:10.1038/nature12486

Ball, K., Edwards, J. D., & Ross, L. A. (2007). The impact of speed of processing training on cognitive and everyday functions. *The Journals of Gerontology. Series B, Psychological Sciences and Social Sciences*, *62 Spec No*(I), 19–31. http://www.ncbi.nlm.nih.gov/pubmed/17565162

Ballesteros, S., Kraft, E., Santana, S., & Tziraki, C. (2015a). Maintaining older brain functionality: A targeted review. *Neuroscience and Biobehavioral Reviews, 55,* 453–477. doi:10.1016/j.neubiorev.2015.06.008

Ballesteros, S., Mayas, J., Prieto, A., Toril, P., Pita, C., Ponce de León, L., et al. (2015b). A randomized controlled trial of brain training with non-action video games in older adults: Results of the 3-month follow-up. *Frontiers in Aging Neuroscience, 7,* 1–12. doi:10.3389/fnagi.2015.00045

Bamidis, P. D., Fissler, P., Papageorgiou, S. G., Zilidou, V., Konstantinidis, E. I., Billis, A. S., et al. (2015). Gains in cognition through combined cognitive and physical training: The role of training dosage and severity of neurocognitive disorder. *Frontiers in Aging Neuroscience, 7,* 1–15. doi:10.3389/fnagi.2015.00152

Barnhoorn, J. S., Haasnoot, E., Bocanegra, B. R., & van Steenbergen, H. (2014). QRTEngine: An easy solution for running online reaction time experiments using Qualtrics. *Behavior Research Methods, 47,* 918–929. doi:10.3758/s13428-014-0530-7.

Basak, C., Boot, W. R., Voss, M. W., & Kramer, A. F. (2008). Can training in a real-time strategy video game attenuate cognitive decline in older adults? *Psychology and Aging, 23*(4), 765–777. doi:10.1037/a0013494

BBC News. (2005). Runner, 94, finishes capital race. http://news.bbc.co.uk/go/pr/fr/?/2/hi/uk_news/scotland/4084162.stm

Bherer, L., Kramer, A. F., Peterson, M. S., Colcombe, S., Erickson, K., & Becic, E. (2006). Testing the limits of cognitive plasticity in older adults : Application to attentional control. *123*, 261–278. doi:10.1016/j.actpsy.2006.01.005

Bialystok, E., Craik, F. I. M., & Luk, G. (2012). Bilingualism: Consequences for mind and brain. *Trends in Cognitive Sciences, 16*(4), 240–249. doi:10.1016/j.tics.2012.03.001.

Bidelman, G. M., & Alain, C. (2015). Musical training orchestrates coordinated neuroplasticity in auditory brainstem and cortex to counteract age-related declines in categorical vowel perception. *The Journal of Neuroscience, 35*(3), 1240–1249. doi:10.1523/JNEUROSCI.3292-14.2015

Boot, W. R., Blakely, D. P., & Simons, D. J. (2011). Do action video games improve perception and cognition? *Frontiers in Psychology, 2,* 226. doi:10.3389/fpsyg.2011.00226.

Bracht, G. H., & Glass, G. V. (1968). The external validity of experiments. *American Educational Research Journal, 5*(4), 437–474. doi:10.3102/00028312005004437

Breteler, M. M., van Swieten, J. C., Bots, M. L., Grobbee, D. E., Claus, J. J., van den Hout, J. H., et al. (1994). Cerebral white matter lesions, vascular risk factors, and cognitive function in a population-based study: The Rotterdam Study. *Neurology, 44*(7), 1246–1252. doi:10.1212/WNL.44.7.1246

Broadbent, D. E., Cooper, P. F., FitzGerald, P., & Parkes, K. R. (1982). The Cognitive Failures Questionnaire (CFQ) and its correlates. *The British Journal of Clinical Psychology/The British Psychological Society, 21,* 1–16. doi:10.1111/j.2044-8260.1982.tb01421.x

Brown, K. W., & Ryan, R. M. (2003). The benefits of being present: Mindfulness and its role in psychological well-being. *Journal of Personality and Social Psychology, 84*(4), 822–848. doi:10.1037/0022-3514.84.4.822

Buitenweg, J. I. V., Murre, J. M. J., & Ridderinkhof, K. R. (2012). Brain training in progress: A review of trainability in healthy seniors. *Frontiers in Human Neuroscience, 6,* 183. doi:10.3389/fnhum.2012.00183

Burton, C. L., Strauss, E., Bunce, D., Hunter, M. A., & Hultsch, D. F. (2009). Functional abilities in older adults with mild cognitive Impairment. *Gerontology, 55*(5), 570–581. doi:10.1159/000228918

Buschkuehl, M., Jaeggi, S. M., Hutchison, S., Perrig-chiello, P., Mu, M., Breil, F., et al. (2008). Impact of working memory training on memory performance in old—Old adults. *Psychology and Aging, 23*(4), 743–753. doi:10.1037/a0014342

Buysse, D. J., Reynolds, C. F., Monk, T. H., Berman, S. R., Kupfer, D. J., III, Reynolds, C. F., et al. (1989). The Pittsburgh sleep quality index: A new instrument for psychiatric practice and research. *Psychiatry Research, 28*(2), 193–213. doi:10.1016/0165-1781(89)90047-4

Central Bureau for Statistics. (2014). Statistics Netherlands: Internetgebruik ouderen fors toegenomen. https://www.cbs.nl/nl-nl/nieuws/2013/50/internetgebruik-ouderen-fors-toegenomen

Colcombe, S. J., Kramer, A. F., Erickson, K. I., Scalf, P., McAuley, E., Cohen, N. J., et al. (2004). Cardiovascular fitness, cortical plasticity, and aging. *Proceedings of the National Academy of Sciences of the United States of America, 101*(9), 3316–3321. doi:10.1073/pnas.0400266101

Colzato, L. S., van Muijden, J., Band, G. P. H., & Hommel, B. (2011). Genetic modulation of training and transfer in older adults: BDNF Val 66Met polymorphism is associated with wider useful field of view. *Frontiers in Psychology, 2,* 1–6. doi:10.3389/fpsyg.2011.00199

Craig, C. L., Marshall, A. L., Sjöström, M., Bauman, A. E., Booth, M. L., Ainsworth, B. E., et al. (2003). International physical activity questionnaire: 12-country reliability and validity. *Medicine and Science in Sports and Exercise, 35*(8), 1381–1395. doi:10.1249/01.MSS.0000078924.61453.FB

Ellison, N. B., Steinfield, C., & Lampe, C. (2007). The benefits of facebook "friends": Social capital and college students' use of online social network sites. *Journal of Computer-Mediated Communication, 12*(4), 1143–1168. doi:10.1111/j.1083-6101.2007.00367.x

Erickson, K. I., Prakash, R. S., Voss, M. W., Chaddock, L., Hu, L., Morris, K. S., et al. (2009). Aerobic fitness is associated with hippocampal volume in elderly humans. *Hippocampus, 19,* 1030–1039. doi:10.1002/hipo.20547

Fillit, H. M., Butler, R. N., O'Connell, A. W., Albert, M. S., Birren, J. E., Cotman, C. W., et al. (2002). Achieving and maintaining cognitive vitality with aging. *Mayo Clinic Proceedings, 77*(7), 681–696. doi:10.4065/77.7.681

Finn, M., & McDonald, S. (2011). Computerised cognitive training for older persons with mild cognitive impairment: A pilot study using a randomised controlled trial design. *Brain Impairment, 12*(3), 187–199. doi:10.1375/brim.12.3.187

Gajewski, P. D., & Falkenstein, M. (2012). Training-induced improvement of response selection and error detection in aging assessed by task switching: Effects of cognitive, physical, and relaxation training. *Frontiers in Human Neuroscience, 6,* 1–18. doi:10.3389/fnhum.2012.00130

Gard, T., Hölzel, B. K., & Lazar, S. W. (2014). The potential effects of meditation on age-related cognitive decline: A systematic review. *Annals of the New York Academy of Sciences, 1307*(1), 89–103. doi:10.1111/nyas.12348

Hedden, T., & Gabrieli, J. D. E. (2004). Insights into the ageing mind: A view from cognitive neuroscience. *Nature Reviews Neuroscience, 5*(2), 87–96. doi:10.1038/nrn1323

Hertzog, C., Kramer, A. F., Wilson, R. S., & Lindenberger, U. (2009). Enrichment effects on adult cognitive development. *Psychological Science, 9*(1), 1–65.

Hommel, B. (1993). The relationship between stimulus processing and response selection in the Simon task: Evidence for a temporal overlap. *Psychological Research, 55*(4), 280–290. doi:10.1007/BF00419688

Inquisit. (2014). *Inquisit 4.0.8.0.* Seattle, WA: Millisecond Software.

Jeste, D. V., Savla, G. N., Thompson, W. K., Vahia, I. M. D., Glorioso, D. K., Martin, A. S., et al. (2014). Older age is associated with more successful aging: Role of resilience and depression. *American Journal of Psychiatry, 170*(2), 188–196. doi:10.1176/appi.ajp.2012.12030386.Older

Karayanidis, F., Coltheart, M., Michie, P. T., & Murphy, K. (2003). Electrophysiological correlates of anticipatory and poststimulus components of task switching. *Psychophysiology, 40*, 329–348. http://www.ncbi.nlm.nih.gov/pubmed/12946108

Karbach, J., & Kray, J. (2009). How useful is executive control training? Age differences in near and far transfer of task-switching training. *Developmental Science, 12*(6), 978–990. doi:10.1111/j.1467-7687.2009.00846.x

Kirchner, W. K. (1958). Age differences in short-term retention of rapidly changing information. *Journal of Experimental Psychology, 55*(4), 352–358. doi:10.1037/h0043688

Lampit, A., Hallock, H., & Valenzuela, M. (2014). Computerized cognitive training in cognitively healthy older adults: A systematic review and meta-analysis of effect modifiers. *PLoS Medicine, 11*(11), 1–18. doi:10.1371/journal.pmed.1001756

Lövdén, M., Brehmer, Y., Li, S.-C., & Lindenberger, U. (2012). Training-induced compensation versus magnification of individual differences in memory performance. *Frontiers in Human Neuroscience, 6,* 1–14. doi:10.3389/fnhum.2012.00141

Lustig, C., Shah, P., Seidler-Dobrin, R. D., & Reuter-Lorenz, P. A. (2009). Aging, training, and the brain: A review and future directions. *Neuropsychology Review, 19,* 504–522. doi:10.1007/s11065-009-9119-9

Nielsen, J. (1994). *Usability Engineering*. Boston, MA: Academic Press Inc.

Owen, A. M., Hampshire, A., Grahn, J. A., Stenton, R., Dajani, S., Burns, A. S., et al. (2010). Putting brain training to the test. *Nature, 465*(7299), 775–778. doi:10.1038/nature09042

Peretz, C., Korczyn, D., & Shatil, E. (2011). Computer-based, personalized cognitive training versus classical computer games: A randomized double-blind prospective trial of cognitive stimuluation. *Neuroepidemiology, 36,* 91–99. doi:10.1159/000323950

Rahe, J., Becker, J., Fink, G. R., Kessler, J., Kukolja, J., Rahn, A., et al. (2015). Cognitive training with and without additional physical activity in healthy older adults: Cognitive effects, neurobiological mechanisms, and prediction of training success. *Frontiers in Aging Neuroscience, 7,* 1–15. doi:10.3389/fnagi.2015.00187

Salthouse, T. A. (2009). When does age-related cognitive decline begin? *Neurobiology of Aging, 30*(4), 507–514. doi:10.1016/j.neurobiolaging.2008.09.023

Schaie, K. W. (1994). The course of adult intellectual development. *The American Psychologist, 49*(4), 304–313. doi:10.1037/0003-066X.49.4.304

Schmuckler, M. A. (2001). What is ecological validity? A dimensional analysis. *Infancy, 2*(4), 419–436. doi:10.1207/S15327078IN0204_02

Schubert, T. W., Murteira, C., Collins, E. C., & Lopes, D. (2013). ScriptingRT: A software library for collecting response latencies in online studies of cognition. *PLoS ONE, 8*(6), 67769. doi:10.1371/journal.pone.0067769

Smith, G. E., Housen, P., Yaffe, K., Ruff, R., Kennison, R. F., Mahncke, H. W., et al. (2009). A cognitive training program based on principles of brain plasticity: Results from the improvement in memory with plasticity-based adaptive cognitive training (IMPACT) study. *Journal of the American Geriatrics Society, 57*(4), 594–603. doi:10.1111/j.1532-5415.2008.02167.x

Sternberg, D. A., Ballard, K., Hardy, J. L., Katz, B., Doraiswamy, P. M., & Scanlon, M. (2013). The largest human cognitive performance dataset reveals insights into the effects of lifestyle factors and aging. *Frontiers in Human Neuroscience, 7,* 1–10. doi:10.3389/fnhum.2013.00292

Theill, N., Schumacher, V., Adelsberger, R., Martin, M., & Jäncke, L. (2013). Effects of simultaneously performed cognitive and physical training in older adults. *BMC Neuroscience, 14,* 1–14. doi:10.1186/1471-2202-14-103

UNFPA and HelpAge. (2012). *Ageing in the Twenty-First Century:A Celebration and AChallenge*. *United Nations Population Fund*. http://link.springer.com/chapter/10.1007/978-3-662-04375-2_2

Voss, M. W., Nagamatsu, L. S., Liu-ambrose, T., & Kramer, A. F. (2011). Exercise, brain, and cognition across the life span. *Journal of Applied Physiology, 111,* 1505–1513. doi:10.1152/japplphysiol.00210.2011

Westendorp, R. (2015). *Growing older without feeling old: On vitality and ageing*. Melbourne: Scribe.

Whitlock, L. A., McLaughlin, A. C., & Allaire, J. C. (2012). Individual differences in response to cognitive training: Using a multi-modal, attentionally demanding game-based intervention for older adults. *Computers in Human Behavior, 28*(4), 1091–1096.

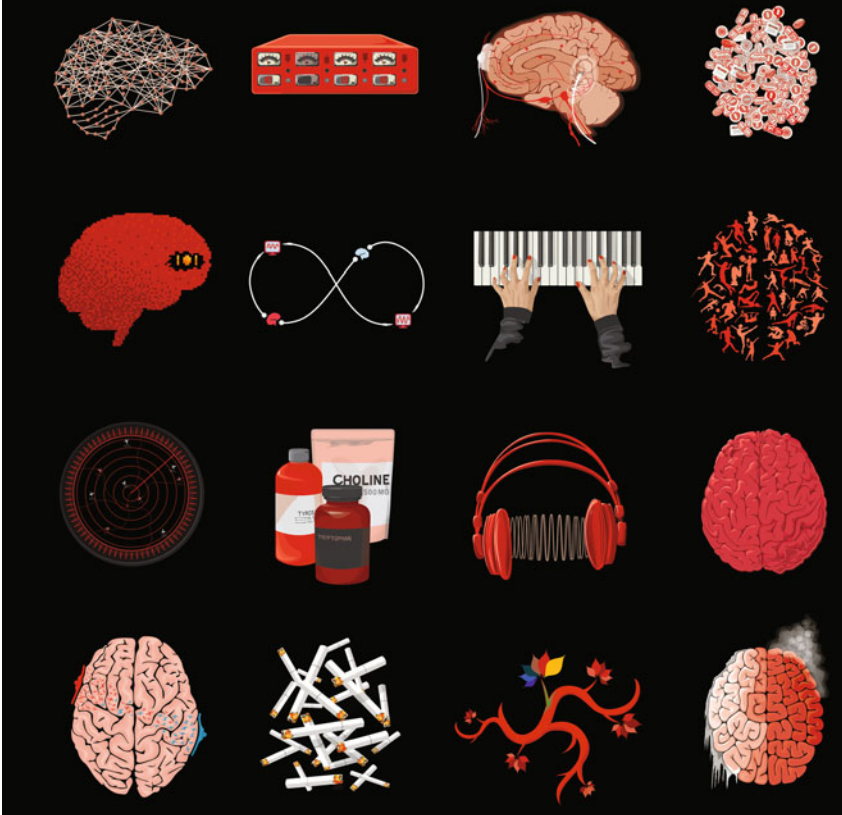
World Health Organization. (2011). Global Health and Aging. *NIH Publication No 117737*, *1*(4), 273–277. http://links.jstor.org/sici?sici=0095-9006(196024)1:4<273:HAA>2.0.CO;2-C

Yaffe, K., Fiocco, A. J., Lindquist, K., Vittinghoff, E., Simonsick, E. M., Newman, A. B., et al. (2009). Predictors of maintaining cognitive function in older adults. *Neurology, 72*(23), 2029–2035. doi:10.1212/WNL.0b013e3181a92c36

Zajonc, R. B. (1965). Social Facilitation. *Science, 149,* 269–274. doi:10.1126/science.149.3681.269

outlook

theory-driven cognitive enhancement: costs and benefits



Part VIII
Outlook

Theory-Driven Cognitive Enhancement: Costs and Benefits

Lorenza S. Colzato

Introduction

This chapter concludes the broad overview of cognitive enhancing methods that this book aims to provide. How far can cognitive enhancement lead use? What are the upcoming challenges? These are the questions that I will address in this final chapter. I will do so by explaining why more specific, mechanistic theories will be necessary to guide the development of successful cognitive enhancing programs and why it is important to take into account the potential mental costs associated with cognitive enhancement. I will also emphasize the importance of considering individual differences and discuss the societal and ethical implications of enhancement programs.

The Seduction of Cognitive Enhancement

In the past people have always tried to improve their own intellectual abilities through study, training and hard work. However, since a couple of decades, people are attempting to "shortcut" the required mental effort by using food supplements

L.S. Colzato (✉)
Cognitive Psychology Unit and Leiden Institute for Brain and Cognition, Leiden University, Wassenaarseweg 52, 2333 AK Leiden, The Netherlands
e-mail: colzato@fsw.leidenuniv.nl

L.S. Colzato
Institute of Cognitive Neuroscience, Faculty of Psychology, Ruhr University Bochum, Bochum, Germany

L.S. Colzato, *Theory-Driven Approaches to Cognitive Enhancement*,
DOI 10.1007/978-3-319-57505-6_23

(see Chapters "Tyrosine"–"Choline"), psychostimulants drugs (see Chapter "Caffeine"–"Modafinil"), noninvasive brain stimulation techniques (see Chapters "Transcranial direct current stimulation" and "Transcutaneous vagus and trigeminal nerve stimulation") or video games (see Chapter "Video games"), to cite only a few enhancing methods. These "individualistic" tendencies go hand-in-hand with ideological developments in public opinion and within political parties, which in many countries have gravitated towards more neoliberal, individualism-heavy positions over the past 15 years or so. Also, industry and funding agencies have taken notice of the many opportunities these enhancing techniques can bring, and the current European Research Area (ERA in Horizon 2020) has various calls to promote, for example, gamification. Indeed, the widespread use of smart phones has led to a real explosion of "apps" to enhance cognitive functioning, ranging from simple alerts reminding the elderly to take her/his pill to theoretically guided programs to systematically enhance specific cognitive functions. Turning psychological experiments and training procedures into apps is certainly handy for both researchers and users, especially as it facilitates integration of cognitive enhancing programs and real-life circumstances. Another example to demonstrate how ERA is focusing on cognitive enhancement is the Joint Programming Initiative 'A healthy diet for a healthy life' which is funding research on how nutrients can prevent (social-) cognitive decline in normal aging. This initiative is particularly emblematic of how economic problems of the welfare system have boosted the interest in procedures and activities that make welfare societally more affordable.

Theory-Driven Cognitive Enhancement

In the past, the field of cognitive enhancement used mainly effect-driven approaches (that seek to demonstrate that an enhancing intervention can have an effect without explaining how it modulates the targeted function and why some people benefit more than others), whereas this book pursued a mechanistically oriented, theory-driven approach that tries to understand and explain individual differences to a degree that allows a comprehensive understanding of how and why a particular intervention enhances (social) cognition. Only such a mechanistically oriented, theory-driven approach will allow for the design of individualized cognitive-enhancement interventions required to make such interventions successful for the recipient at an individual level, and to make welfare more affordable at a societal level.

Individualized Cognitive-Enhancement Interventions

Most cognitive enhancing programs have a one-size-fits-all design and presuppose that people benefit from the intervention more or less the same way and to more or less the same degree.

However, there is abundant evidence suggesting this is not always plausible. I propose that the efficiency of cognitive enhancing interventions will often be modulated by inter-individual differences, including pre-existing neuro-developmental factors and differences with a genetic basis. Accordingly, only enhancing programs that are tailored to individual abilities, skills, and needs are likely to succeed.

The reason why it is crucial to take into account individual improvements is that the functions relating psychological functions (and/or their neural underpinnings) to performance are often not linear. For instance, many neurotransmitters relate to performance in a nonlinear (inverted-U-type) fashion, with best performance related to a medium level, and dopamine is no exception. Hence, increasing the dopaminergic level too much is likely to be counterproductive, as this may drive individuals over and above their point of optimality. In a nutshell, I suggest that the effectivity of cognitive enhancing interventions based on supplements or drugs acting on dopamine might be modulated by the genetic variability related to dopaminergic polymorphisms. Consistent with this hypothesis, as pointed out in Chapter "Tyrosine", a recent study took into account individual differences (i.e., genetic differences) in base levels of dopamine to explain the effectivity of the food supplement tyrosine, the chemical precursor of dopamine. Indeed, it is likely that depending on this dopamine baseline levels, some people may benefit more than others from tyrosine intake (Jongkees et al. 2014). The study showed evidence supporting the idea that tyrosine supplementation may function as a cognitive enhancer and compensate for unfavorable genetic predisposition (Colzato et al. 2016). Tyrosine was administered to participants genotyped for the C957T polymorphism and the DRD2 gene (a polymorphism related to the striatal dopamine level). Measures of working memory updating and inhibitory control were acquired. T/T homozygotes (i.e., individuals associated with lower striatal dopamine level) showed larger beneficial effects of tyrosine supplementation than C/C homozygotes (i.e., individuals associated with higher striatal dopamine level). These findings reinforce the idea that genetic predisposition modulates the effect of tyrosine in its role as cognitive enhancer (Jongkees et al. 2014; Colzato et al. 2016).

Along the same line in Chapter "Modafinil", a pharmacological study showed that effects of Modafinil on waking functions after sleep loss are determined by catechol-*O*-methyltransferase (COMT) genotype (Bodenmann et al. 2009). Catechol-*O*-methyltransferase is an enzyme that catalyzes the breakdown of dopamine in the cerebral cortex. Given that Modafinil increases dopamine level in the brain, the authors investigated whether the functional $Val^{158}Met$ polymorphism contributes to individual differences in the reactivity to Modafinil administration. The findings revealed that Val/Val homozygotes (i.e., individuals potentially associated with lower frontal dopamine level) showed larger beneficial effects of Modafinil administration than Met/Met homozygotes (i.e., individuals potentially associated with higher frontal dopamine level), suggesting that genetically determined differences in dopamine function may explain inter-individual differences in response to Modafinil administration.

Another technique for which the effectivity of cognitive enhancement depends on pre-existing differences at the genetic level is game-based intervention. Participants were genotyped for the COMT Val^{158}Met polymorphism and trained on playing "Half-Life 2", a first-person shooter game that has been shown to improve cognitive flexibility. Pre-training (baseline) and post-training measures of cognitive flexibility were acquired by means of a task-switching paradigm. As predicted, Val/Val homozygous individuals (i.e., individuals with a beneficial genetic predisposition for cognitive flexibility) showed larger beneficial transfer effects than Met/-carriers, supporting the possibility that genetic predisposition modulates transfer effects and that this game-based intervention promotes cognitive flexibility in individuals with a suitable genetic predisposition (Colzato et al. 2014). Even if this study needs to be replicated with a larger sample size, it can be considered together with the other studies highlighted above, as proof-of-principle that highlights the importance of considering individual differences.

Considering these differences and assessing how they interact with different cognitive enhancing interventions will allow for the development of personalized, individually tailored training programs. Not only will these programs be more effective but they also will be much more motivating for participants (as unnecessary failures due to person-method mismatches can be avoided) and more cost efficient. This in turn will make the implementation of such interventions more likely even in times of sparse budgets. In view of the rapid aging of European societies, the number of potential beneficiaries of such an individualized approach is dramatically increasing, and the societal need for maximizing the human cognitive potential in the elderly will grow further as the economic situation will require extensions of the working lifetime.

Cognitive Side Effects of Cognitive Enhancement

Unfortunately, every coin has two sides and cognitive enhancement may not only be associated with mental benefits but also with mental losses.

Iuculano and Kadosh (2013) were the first to point out, in the field of brain stimulation, that research so far has primarily focused on optimizing protocols for effective stimulation while disregarding the possibility of cognitive side effects. In this section, I will argue that this assumption does not only apply to tDCS (see Chapter "Transcranial Direct Current Stimulation") but also to other cognitive enhancing techniques, such as some pharmacological intervention (i.e., Modafinil —Chapter "Modafinil") and meditation (see Chapter "Meditation").

The seminal study by Iuculano and Kadosh (2013) showed in an impressive manner that cognitive enhancement through tDCS can happen at the cost of other cognitive functions. Indeed, the authors found a clear dissociation that supports this claim: active tDCS to the posterior parietal cortex improved numerical learning, whereas automaticity for the learned material was compromised. In contrast, active tDCS stimulation to the dorsolateral prefrontal cortex decreased the learning

process, whereas automaticity for the learned material was facilitated. These results are very fascinating because, compared to sham stimulation, they show a concurrent cognitive enhancement and cognitive impairment.

Similarly to these tDCS results, in sleep-deprived adults, Modafinil seems to maintain and restore performance on cognitive tasks, but at the possible cost of subjective overconfidence. Indeed, studies have shown that smaller doses of Modafinil seem to be effective at maintaining cognitive performance, or at a single, large dose to restore the same performance to near-baseline levels in people fatigued due to lack of sleep (Stivalet et al. 1998; Whitmore et al. 2004, 2006). However, these cognitive benefits may come at a price: subjects' estimates of their own cognitive performance exceeded their actual performance. That is, the capability to assess one's own performance accurately may be negatively affected through the use of Modafinil (Baranski and Pigeau 1997; Batejat and Lagarde 1999; Gurtman et al. 2008).

Another cognitive enhancement technique to which the idea that cognitive enhancement produces cognitive side effects may apply is meditation. As pointed out in Chapter "Meditation", given that open monitoring meditation facilitates a control state that promotes quick "jumps" from one thought to another by reducing the top-down control of cognitive processing, this meditation type facilitates performance in tasks that rely on cognitive flexibility, but it also impairs performance in tasks that rely on cognitive stability. In contrast, given that focused attention meditation is assumed to increase top-down control leading to greater control strength (i.e., concentration on the goal), this meditation type improves performance in tasks that depend on cognitive stability, but it also impairs performance in tasks that depend on cognitive flexibility.

In the future, in order to further investigate whether cognitive side effects of cognitive enhancement will take place in other cognitive enhancing techniques, it will be crucial to include additional tasks in each enhancing study. By doing so, it will be possible to unravel whether the costs associated with cognitive enhancement follow a general pattern or might be specific to some types of enhancing techniques. Accordingly, it is important that future studies aimed at improving performance will focus not only on the matter of cognitive enhancement, but also on the potential costs that go with it. As pointed out by Iuculano and Kadosh (2013), one crucial factor will be to understand the neurobiological factors that might determine the balance between cognitive enhancement and impairment. Indeed, only when we will be able to understand the connection between enhancement and its putative side effects, we will learn how to avoid these mental costs or compensate for them.

Neuroethical Issues in Cognitive Enhancement

Cognitive enhancement is one of the most widely discussed topics in neuroethics (Bostrom and Sandberg 2009). In this section I will discuss two ethical aspects that I expect to dominate future discussions. The first has to do with the "honesty" of the

intervention. For instance, it has been pointed out that methods of cognitive enhancement may disrespect dignity and human nature, augment inauthenticity and cheating behavior, and may encourage an uncontrolled striving for excellence and perfection (Habermas 2003; Kass 2002). Such thoughts are not far-fetched, as demonstrated by the increasing use of cognitive enhancing drugs, such as Modafinil (see Chapter "Modafinil") and Ritalin (see Chapter "Ritalin"), by students to boost their academic performance. Soon, universities may opt to prohibit drug use altogether, or to tolerate it in some situations (exams). The same reasoning is also applicable to commercial brain stimulation devices, which are available on the internet without any restrictions (Steenbergen et al. 2016).

A second issue relies instead on the tension between two widely shared ethical principles underlying our society: individual freedom and equality. While effective cognitive enhancing programs can be taken to support the expression of individual freedom, it may clash with equality. Societies and upward mobility in particular rely increasingly on competition, which emphasizes individual performance and abilities. Cognitive enhancement is likely to produce "positional benefits" by improving one's social and economic status as compared to others. While this could be considered a fair individual choice, it may have consequences for general public expectations and standards. Once a number of individuals have shown that it is possible to improve one's cognitive abilities, public pressure on other individuals could arise to augment their abilities as well. The existence of effective cognitive enhancing programs could thus generate or increase the pressure of always being the "king of mountain", to work harder, longer, and more intensively, which in the end may aggravate the problems one was initially aiming to solve. Strictly speaking, the simple option to enhance one's cognitive abilities could increase social competition. Worse, as the probability to profit from cognitive enhancing interventions may differ between individuals, the availability of enhancing programs may contribute to the emergence, and increase the size of, societal gaps (Bostrom and Sandberg 2009).

Counter-arguments exist for both of these ethical issues. Even though several enhancing methods rest on the same cognitive and neural mechanisms, some are considered more societally acceptable than others. For instance, both the food supplement tyrosine (see Chapter "Tyrosine") and Ritalin (see Chapter "Ritalin") act on dopamine levels and are aimed at enhancing memory functions, but integrating a diet with tyrosine is considered a healthy choice, whereas taking Ritalin is regarded by many as a cheating behavior.

Second, cognitive enhancing interventions could be used as a way of decreasing, rather than increasing societal/social inequalities by allowing all, and not just the economically privileged individuals to fully achieve their cognitive potential. This would not eradicate competition but generate more equal terms (Savulescu 2009). Further, it is important to consider that the widespread use of cognitive enhancing methods and the associated cognitive benefits might have important social benefits. Indeed, some studies estimate that augmenting the average IQ of the world population by no more than 3% would reduce poverty rates by 25% (Schwartz 1994) and

result in an annual economic gain of US$165–195 billion and 1.2–1.5% of the national gross domestic product (Salkever 1995).

Conclusion

This conclusive chapter pointed to the need to develop more specific, mechanistic theories to guide cognitive enhancing programs and to understand the possible mental costs associated with them. Only understanding the mechanisms behind cognitive enhancement will allow compensation for the mental costs and designing individualized cognitive enhancement interventions. Cognitive enhancement is not just one more psychological intervention but it touches upon important societal and ethical issues. Accordingly, researchers in this field will be required to actively interact with funding agencies, companies and politics to make sure that both risks and promises of cognitive enhancement are realistically assessed.

References

Baranski, J. V., & Pigeau, R. (1997). Self-monitoring cognitive performance during sleep deprivation: Effects of Modafinil, d-amphetamine and placebo. *Journal of Sleep Research, 6,* 84–91.

Batejat, D., & Lagarde, D. (1999). Naps and Modafinil as countermeasures for the effects of sleep deprivation on cognitive performance. *Aviation, Space and Environmental Medicine, 70*(5), 493–498.

Bodenmann, S., Xu, S., Luhmann, U. F. O., Arand, M., Berger, W., Jung, H. H., et al. (2009). Pharmacogenetics of modafinil after sleep loss: Catechol-*O*-methyltransferase genotype modulates waking functions but not recovery sleep. *Clinical Pharmacology and Therapeutics, 85*(3), 296–304.

Bostrom, N., & Sandberg, A. (2009). Cognitive enhancement: Methods, ethics, regulatory challenges. *Science and Engineering Ethics, 15*(3), 311–341.

Colzato, L. S., van den Wildenberg, W., & Hommel, B. (2014). Cognitive control and the COMT Val158Met polymorphism: Genetic modulation of videogame training and transfer to task-switching efficiency. *Psychological Research, 78*, 670–678.

Colzato, L. S., Steenbergen, L., Sellaro, R., Stock, A. K., Arning, L., & Beste, C. (2016). Effects of L-tyrosine on working memory and inhibitory control are determined by DRD2 genotypes: A randomized controlled trial. *Cortex, 82,* 217–224.

Gurtman, C. G., Broadbear, J. H., & Redman, J. R. (2008). Effects of Modafinil on simulator driving and self-assessment of driving following sleep deprivation. *Human Psychopharmacology: Clinical and Experimental, 23,* 681–692.

Habermas, J. (2003). *The future of human nature*. Cambridge: Polity Press.

Iuculano, T., & Kadosh, R. C. (2013). The mental cost of cognitive enhancement. *The Journal of Neuroscience, 33*(10), 4482–4486.

Jongkees, B. J., Hommel, B., & Colzato, L. S. (2014). People are different: Tyrosine's modulating effect on cognitive control may depend on individual differences related to dopamine function. *Frontiers in Psychology, 5,* 1101.

Kass, L. (2002). *Life, liberty, and defense of dignity: The challenge for bioethics*. San Francisco: Encounter Books.

Salkever, D. S. (1995). Updated estimates of earnings benefits from reduced exposure of children to environmental lead. *Environmental Research, 70,* 1–6.

Savulescu, J. (2009). Enhancement and fairness. In P. Healey (Ed.), *Tomorrow's people: The challenges of technologies for life-extension and enhancement*. London: Earthscan.

Schwartz, J. (1994). Low-level lead exposure and children's IQ: A meta-analysis and search for a threshold. *Environmental Research, 65,* 42–55.

Steenbergen, L., Sellaro, R., Hommel, B., Kühn, S., & Colzato, L. S. (2016). "Unfocus" on foc.us: Commercial tDCS headset impairs working memory. *Experimental Brain Research, 234,* 637–643.

Stivalet, P., Esquivié, D., Barraud, P., Leifflen, D., & Raphel, C. (1998). Effects of Modafinil on attentional processes during 60 hours of sleep deprivation. *Human Psychopharmacology, 13* (7), 501–507.

Whitmore, J., Doan, B., Fischer, J., French, J., & Heintz, T. (2004). *The efficacy of Modafinil as an operational fatigue countermeasure over several days of reduced sleep during a simulated escape and evasion scenario* (No. AFRL-HE-BR-TR-2002-0021). Air Force Research Lab Brooks AFB TX Human Effectiveness DIR/Biodynamics and Protection DIV.

Whitmore, J., Hickey, P., Doan, B., Harrison, R., Kisner, J., Beltran, T., et al. (2006). *A double-blind placebo-controlled investigation of the efficacy of Modafinil for maintaining alertness and performance in sustained military ground operations*. Air Force Research Lab Brooks AFB TX Human Effectiveness DIR/Biodynamics and Protection DIV.

Retraction Note to: Theory-Driven Approaches to Cognitive Enhancement

Lorenza S. Colzato

Retraction Note to:
L.S. Colzato, *Theory-Driven Approaches to Cognitive Enhancement*, https://doi.org/10.1007/978-3-319-57505-6

The Editors have retracted the chapters (1, 2, 13 and 16) because of serious research integrity issues. All of the chapter authors agree to this retraction

Chapter 1 – Tyrosine, pages 5–16

The Publisher has retracted this Chapter. After publication, concerns were raised regarding substantial text overlap with a previous article [1]. The first author of [1] is not included in the authorship of this chapter.

Lorenza S. Colzato does not agree to this retraction.

[1] Jongkees, B. J., Hommel, B., Kühn, S., & Colzato, L. S. Effect of tyrosine supplementation on clinical and healthy populations under stress or cognitive demands—A review. *Journal of psychiatric research* **70**, 50-57 (2015). https://doi.org/10.1016/j.jpsychires.2015.08.014

Chapter 2 – Tryptophan, pages 17–30

The Publisher has retracted this Chapter. After publication, concerns were raised regarding substantial text overlap with a previous article [1]. None of the co-authors of [1] are included in the authorship of this chapter.

Martin Reuter and Peter Kirsch agree to this retraction. Lorenza S. Colzato does not agree to this retraction. Ana Beatriz Rodríguez Moratinos has not responded to any correspondence from the editor or publisher about this retraction.

The retracted versions of these chapters can be found at
https://doi.org/10.1007/978-3-319-57505-6_1
https://doi.org/10.1007/978-3-319-57505-6_2
https://doi.org/10.1007/978-3-319-57505-6_13
https://doi.org/10.1007/978-3-319-57505-6_16

L.S. Colzato, *Theory-Driven Approaches to Cognitive Enhancement*,
https://doi.org/10.1007/978-3-319-57505-6_24

[1] Steenbergen, L., Jongkees, B. J., Sellaro, R., & Colzato, L. S. Tryptophan supplementation modulates social behavior: a review. *Neuroscience & Biobehavioral Reviews* **64**, 346-358 (2016). https://doi.org/10.1016/j.neubiorev.2016.02.022

Chapter 13– Musical Training, pages 187–198

The Publisher has retracted this Chapter. After publication, concerns were raised regarding substantial text overlap with a previous article [1]. None of the co-authors of [1] are included in the authorship of this chapter.

Lorenza S. Colzato does not agree to this retraction.

[1] Benz, S., Sellaro, R., Hommel, B., & Colzato, L. S. Music Makes the World Go Round: The Impact of Musical Training on Non-musical Cognitive Functions-A Review. *Frontiers in psychology* **6**, 2023 (2016). https://doi.org/10.3389/fpsyg.2015.02023

Chapter 16 – Meditation, pages 225–237

The Publisher has retracted this Chapter. After publication, concerns were raised regarding substantial text overlap with a previous article [1]. The first author of [1] is not included in the authorship of this chapter.

Lorenza S. Colzato does not agree to this retraction. Bernhard Hommel has not explicitly stated whether they agree to this retraction notice.

[1] Lippelt, D. P., Hommel, B., & Colzato, L. S. (2014). Focused attention, open monitoring and loving kindness meditation: effects on attention, conflict monitoring, and creativity - A review. Frontiers in psychology, 5, 1083.

Index

L.S. Colzato, *Theory-Driven Approaches to Cognitive Enhancement*,
DOI 10.1007/978-3-319-57505-6