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CONTENTS

Dear reader of our Maastricht Student Journal of Psychology and Neuroscience,

In front of you is volume 10 of our Maastricht Student Journal of Psychology and Neuroscience. This journal is represents a reflection of student writing at the Faculty of Psychology and Neuroscience. The journal's aim is to spreading creative ideas, which typically arise from young brains, and to provide students with the valuable experience of both publishing and reviewing scientific articles. The journal results from a publishing process performed (mostly) by students. Publishing as a student requires going through the process of receiving feedback, rethinking your work, adjusting it, and resubmitting it. Such a format of the publishing process is also used by peer reviewed scientific journals. The experience is aimed at giving students a head start in publishing. In addition, peer reviewing papers provides the opportunity to be critical on someone else's writing, which possibly makes you susceptible to spotting room for improvement in your own writing. Therefore, the journal enables students to be better scientific writers and generate scientific ideas.

The efforts of the student authors, student reviewers and staff editorial board has resulted in the current edition of our journal in which, among others, popular topics like health and psychedelic medicine are discussed. *Hanna Hoogen* reviews the literature to answer the question if regular physical resistance training has a positive impact of the ability of the body to manage oxidative stress. *Lou Antoinette Godvliet* explored the idea of combining hypnotherapie and psychedelic medicine to treat addiction and comorbid disorders. The author provides evidence for the efficacy,

which is greater that either treatments alone. *Kim Carina Hoffmann* takes a deeper dive into neurobiological mechanisms, by investigating the role of Ca^{2+}-ion influx amplitude into the post-synaptic neuron in long-term potentiation and long-term depression. The author proposes that the amplitude may be one of the decisive factors in determining the onset of long-term potentiation or long-term depression. Finally, *Dubberstein, Grashoff, Hofmann, Kaiser, Kan, Kothe, Stangier, and Zielke* performed and report on an experimental study in which they attempt to test the hypothesis that cognitive decision making relies partly on the emotional context in which the decision is presented. In addition, they utilised fMRI to determine the underlying brain activation.

We hope that this edition provides motivation to students to pursuit publishing their work in our journal, which may be a starting point for a career in science. Finally, we are delighted to be able to provide this platform for spreading creative ideas and being a fertile soil for sprouting scientific interest.

Peter van Ruitenbeek

On behalf of the editorial board,

This paper is the product of students from the Faculty of Psychology and Neuroscience, Maastricht University and is meant for student educational purposes only.

HANNA HOOGEN

Does Resistance Training Have Positive Effects on Redox Homeostasis in the Human Body?

Literature Review

Regular aerobic or resistance training is associated with better body composition, physical and mental health, and reduced all-cause mortality. Physical exercise also lowers the risk for diseases that relate to chronic oxidative stress like cancer, diabetes, and neurodegenerative disorders. Paradoxically, exercise induces oxidative stress in the body. This review investigates whether highly demanding resistance training positively impacts redox homeostasis in the human body. From the studies reviewed here, it can be concluded that regular resistance training results in training adaptations of the antioxidant system, enabling the body to cope better with future oxidative stress induced by exercise or other bodily or environmental factors. This effect has been demonstrated over different ages, genders, health statuses, as well as resistance training intensities. Thus, it should be recommended as a general health behavior for the prevention and potential therapy of a wide range of diseases. This review is limited by

the small number of reviewed studies. Further, a comparison between studies is difficult due to the variety of subjects. Nonetheless, a positive effect of resistance training on redox homeostasis could be consistently reported.

Keywords: oxidative stress, resistance training, physical exercise, redox homeostasis

INTRODUCTION

Does Resistance Training Have Positive Effects on Redox Homeostasis in the Human Body?

It is common knowledge that an active lifestyle with regular physical exercise benefits the health of the body and mind. Physical activity has been related to improved mood and body composition – measured in muscle mass, fat mass, or BMI. In addition, physical activity is associated with a reduction in all-cause mortality, particularly by reducing the risk of common (fatal) diseases like cardiovascular disease, diabetes, cancer, and Alzheimer's disease (Blair et al., 2001; Crespo et al., 2002; Hendrix et al., 2020; Kraemer et al., 2002; Oguma et al., 2002; Penedo & Dahn, 2005; Powers et al., 2020; Westcott, 2012; Winett & Carpinelli, 2001). Many of those common diseases, like cancer, diabetes, as well as neurodegenerative disorders like Parkinson's disease and Alzheimer's disease, are related to chronic oxidative damage (Finaud et al., 2006; Powers et al., 2020; Valko et al., 2007). Excessive oxidative stress causes oxidative damage.

Oxidative stress refers to a disruption of redox homeostasis, referring to the balance between pro-oxidants (oxidizing agents) and antioxidants (reduction agents), due to an increase in pro-oxidants, which has detrimental effects on cell functioning. Pro-oxidants are prone to oxidize other molecules to become more stable. Hence, increases in oxidants that are not sufficiently scavenged by antioxidants results in oxidative damage - the oxidation of proteins,

DNA, and lipids, impairing their function and therefore leading to cell damage or death. Cell damage, especially damage to DNA, can cause mutations and altered gene expression which ultimately induces and perpetuates diseases like cancer (Finaud et al., 2006; Hendrix et al., 2020; Powers et al., 2020; Powers & Jackson, 2008; Valko et al., 2007).

Regular physical exercise has been shown to reduce the risk of diseases related to oxidative stress (Crespo et al., 2002; Powers & Jackson, 2008; Winett & Carpinelli, 2001). Paradoxically, an acute bout of physical exercise increases the generation of reactive oxygen species (ROS), a subset of oxidants that contain oxygen and are highly reactive. ROS, like other pro-oxidants, can damage DNA, lipids, and proteins, by oxidizing them. An increase in ROS, if not sufficiently counteracted by an increase in antioxidants leads to oxidative stress and damage. Previous studies established that any form of physical exercise increases ROS since the contraction of muscles is associated with ROS production. Hence, exercise induces oxidative stress, which can lead to oxidative damage (Powers et al., 2020; Powers & Jackson, 2008). Still, despite, or maybe because of this exercise-induced oxidative stress, physical exercise has many positive effects on physical and mental health. Regular physical exercise induces several positive training adaptations relating to insulin resistance, metabolic rate, body composition, and cardiovascular fitness (Winett & Carpinelli, 2001). These training adaptations might extend to the redox system, leading to higher resilience and antioxidant capacity, and overall better regulation of redox homeostasis. Therefore, exercise could prepare the body to cope with otherwise induced oxidative stress, by "training" the antioxidant response. A trained antioxidant system

could slow or prevent the detrimental effects of disorders associated with oxidative stress, like Alzheimer's, cardiovascular disease, depression, and schizophrenia, as well as slow biological aging (Raza et al., 2016; Valko et al., 2007). In addition, it has been shown that a certain amount of ROS is necessary for cell signaling and immune function. Therefore, only a sustained highly oxidative environment will ultimately have negative effects on health (Finaud et al., 2006; Powers & Jackson, 2008).

To date, most research into exercise was performed on aerobic training, for example, running, swimming, or biking (Dilorenzo et al., 1999; Finaud et al., 2006; Roque et al., 2013; Tarumi & Zhang, 2014; Wilmore, 2003). However, there has been an increasing scientific interest in anaerobic or resistance training (RT). In RT, controlled voluntary muscle movements are performed against resistance, for example, body weight, free weights, or machines. Increasing evidence showed that the health effects of RT are comparable to those associated with aerobic training (Blair et al., 2001; Crespo et al., 2002; Kraemer et al., 2002; Westcott, 2012; Winett & Carpinelli, 2001). Both aerobic training and RT induce oxidative stress (Finaud et al., 2006). Still, both activities lead to considerable health benefits. RT is simple but versatile, efficient, and effective (Winett & Carpinelli, 2001). Therefore, it is highly suitable for health interventions in the general or patient population. Research must investigate which factors contribute to the positive effects of RT on the redox system. This allows a safe implementation of RT interventions for patients with diseases related to oxidative stress.

Firstly, in this review paper, it is explored whether RT leads to training-induced adaptations in the body's redox system and therefore facilitates redox homeostasis and antioxidant response. Secondly, it is investigated whether these benefits occur without additional detrimental effects due to RT-induced oxidative stress. In addition, the effects of RT on different population groups – age, gender, and health status – are compared. Lastly, the influence of RT intensity is evaluated.

Oxidative stress

Oxidative stress can be defined as an increased ratio of pro-oxidants to antioxidants, which impairs redox signaling and control, and/or leads to molecular damage (Powers et al., 2020; Powers & Jackson, 2008). ROS are a subset of pro-oxidants that contain oxygen and have unpaired electrons or are highly unstable. They are highly reactive because they achieve a more stable state by oxidizing other molecules. ROS are prone to oxidize cell or mitochondrial DNA, lipids, and (misfolded) proteins which damages those molecules and impairs their functioning in the cell. This in turn can induce apoptosis, inflammation, or altered cellular function. (Finaud et al., 2006; Valko et al., 2007). The oxidation of lipids in the cell membrane compromises the integrity of the cell and increases membrane permeability. Protein oxidation can damage the structure of proteins and enzymes, thus altering their function and impairing processes like genetic transcription. ROS can also damage DNA and cause strand breaks which increases the chance of harmful mutations and

contributes to cell aging and cancer (Finaud et al., 2006). Oxidative damage has been related to common diseases, including cancer, cardiovascular disease, diabetes, and neurodegenerative diseases, like Parkinson's and Alzheimer's (Finaud et al., 2006; Powers et al., 2020; Valko et al., 2007) as well as mental disorders, like depression, bipolar disorder, and schizophrenia (Raza et al., 2016).

The production of ROS is a byproduct of cell metabolism that occurs naturally in the body. The presence of ROS is not inherently negative and does not inevitably lead to oxidative damage. Research showed that low-to-moderate amounts of ROS are essential for immune function, cell signaling, enzyme activation, drug detoxification, glycogen repletion, apoptosis, and muscle force production (Finaud et al., 2006; Powers et al., 2020; Powers & Jackson, 2008). Therefore, a redox imbalance in favor of the antioxidant side also has detrimental effects on health. For example, it can favor the growth of cancer because cancer cells are inhibited from programmed cell death (apoptosis). ROS are continuously scavenged by bodily enzymatic and non-enzymatic as well as nutritional antioxidants to achieve homeostasis and prevent oxidative damage (Finaud et al., 2006; Powers & Jackson, 2008; Valko et al., 2007). The most commonly investigated antioxidants are superoxide dismutase (SOD), glutathione peroxidases (GPx), catalase (CAT), vitamin C, vitamin E, uric acid, and glutathione (GSH). Therefore, a large increase in ROS production does not necessarily lead to oxidative damage if the ROS are sufficiently counteracted by antioxidants. Thus, it is desirable to have a flexible antioxidant system that can upregulate antioxidant production to accommodate spontaneous increases in ROS while

avoiding continuously high antioxidant levels that prevent the signaling and immune functions of ROS (Powers & Jackson, 2008).

Different markers are used to assess ROS, oxidative damage, and antioxidant capacity. The most widely used markers for oxidative damage are malondialdehyde (MDA) or PEROX for lipid peroxidation, carbonyl groups for protein oxidation, 8-OH-dG for DNA oxidation, and GSH/GSSH ratio for overall oxidative stress (Finaud et al., 2006; Powers & Jackson, 2008; Valko et al., 2007). Measuring ROS directly and reliably is difficult because of their short half-lives. Therefore, most studies use the markers of oxidative damage listed above. For measuring antioxidant capacity, the most common markers are SOD and total antioxidant capacity. The levels of all the antioxidants mentioned above (CAT, GPx, uric acid…) can be directly measured since they are constantly present in cells. In conclusion, the deciding factor for health or disease is the continuous balance between oxidants and antioxidants (redox homeostasis) as well as the total antioxidant capacity in response to spontaneous strong increases in oxidants.

Effects of resistance training on redox homeostasis

Various studies showed that physical activity of any kind increases ROS production, due to increased muscle contractions, cardiovascular activity, and metabolic rate (Belviranli & Gökbel, 2006; Diaba-Nuhoho et al., 2018; Finaud et al., 2006; Hendrix et al., 2020; Hudson et al., 2008; Powers et al., 2020; Powers & Jackson, 2008; Thirupathi et al., 2021). Increased body temperature and lactic acid are also related to the exercise-induced increase in ROS (Finaud et al., 2006). This

exercise-induced oxidative stress can also lead to oxidative damage to proteins, lipids, and DNA. During aerobic exercise, the increased amount of ROS stem mainly from cell mitochondria (Finaud et al., 2006; Powers et al., 2020; Powers & Jackson, 2008; Valko et al., 2007). However, during RT, ROS are additionally produced during ischemia-reperfusion (Finaud et al., 2006). Ischemia-reperfusion occurs when the muscles are highly active – which is especially the case with high-intensity, high-resistance training. Therefore, the blood flow is mainly directed to the muscle fibers, which leaves other tissues ischemic. After tension is released, blood flows back into the ischemic tissues quickly, which increases ROS and can result in tissue injury. Still, it is unclear what causes ROS during ischemia-reperfusion(Finaud et al., 2006).

The production of ROS increases with the intensity and duration of muscle force production. It is important to investigate the effects of RT on the redox system because RT is often performed at high intensities – often higher than aerobic activity – to either gain substantial amounts of muscle mass (hypertrophy), or to increase muscle endurance or strength. Training intensities usually vary between 70-90% of the one-repetition maximum (1RM) – that is the maximum load with which one can perform one repetition of the exercise. This high-intensity training increases the overall strain on multiple body systems, especially the muscle fibers and cardiovascular system. Therefore, higher intensity training should also increase ROS production to a greater extent, which might result in negative consequences. Research showed that with prolonged exercise ROS contribute to muscle fatigue. Furthermore, if exercise is excessive and

nutritional antioxidants are insufficient, exercise-induced oxidative stress can lead to overtraining syndrome (Finaud et al., 2006; Hendrix et al., 2020; Powers & Jackson, 2008). However, despite the potential negative consequences of exercise-induced oxidative stress, ROS are necessary for muscle force production and thus essential for exercise. In addition, the presence or increase of ROS does not necessarily cause oxidative damage if they are sufficiently counteracted by an increase of antioxidants.

Previous research showed that regular aerobic training, and RT, result in several training adaptations which concern body composition, strength, mobility, metabolism, and cardiovascular adaptations (i.e., VO2max increase) (Blair et al., 2001; Bloomer et al., 2008; Kraemer et al., 2002; Powers et al., 2020; Westcott, 2012; Winett & Carpinelli, 2001). These training adaptations possibly extend to the redox system. Since exercise generates ROS through muscle contraction and ischemia-reperfusion it subjects the body to the stimulus of oxidative stress that originates as a by-product of the intense activity of healthy bodily systems (i.e., muscles). Thus, the body can "practice" its antioxidant response in a controlled and repeated way. Therefore, should toxins or diseases induce excessive oxidative stress, the body is prepared to react due to its increased antioxidant capacity. However, the exact mechanisms responsible for the inverse relationship between physical exercise and disorders related to oxidative stress remain elusive. In this review, eleven studies are compared, to investigate whether the training adaptations caused by regular RT include adaptations of the redox system In nine of those studies, subjects that had not performed RT in the past year

participated in an RT intervention (Alikhani & Sheikholeslami-Vatani, 2019; Azizbeigi et al., 2013, 2015; Bloomer et al., 2008; Bobeuf et al., 2011; Cakir-atabek et al., 2010; Cook et al., 2013; Vezzoli et al., 2019; Vincent et al., 2006). The interventions comprised RT two-to-three times a week on non-consecutive days for around one hour, including a warm-up. The interventions lasted between six weeks and six months. The two remaining studies compared existing groups of inactive individuals with those who perform regular RT (Cakir-atabek & Ozdemir, 2015; Diaba-Nuhoho et al., 2018).

Eight studies investigated the effect of RT on markers of lipid peroxidation (MDA (Alikhani & Sheikholeslami-Vatani, 2019; Azizbeigi et al., 2013, 2015; Bloomer et al., 2008; Bobeuf et al., 2011; Cakir-atabek et al., 2010; Diaba-Nuhoho et al., 2018) or PEROX (Vincent et al., 2006)) as an indicator of oxidative damage. In six of those eight studies, RT decreased the investigated marker of lipid peroxidation. One study (Bobeuf et al., 2011) reported no significant difference. A study that compared active with inactive individuals (Diaba-Nuhoho et al., 2018) found increased MDA levels for vigorous exercisers.

To evaluate the body's ability to cope with an increase in ROS, five studies (Alikhani & Sheikholeslami-Vatani, 2019; Azizbeigi et al., 2013; Bloomer et al., 2008; Bobeuf et al., 2011; Vezzoli et al., 2019) assessed total antioxidant capacity (TAC), Trolox equivalent antioxidant capacity (TEAC), or total antioxidant status (TAS). Only two studies (Alikhani & Sheikholeslami-Vatani, 2019; Vezzoli et al., 2019) found an increase in the examined marker, while the rest indicated no difference between exercise or non-exercise groups or

between pre-and post-intervention. Five studies measured SOD as an indicator of antioxidant capacity (Azizbeigi et al., 2013, 2015; Bloomer et al., 2008; Cakir-atabek & Ozdemir, 2015; Diaba-Nuhoho et al., 2018). All found an increase in SOD for the exercise group.

Overall, most of the studies showed a trend toward an increase in antioxidants, as well as a decrease in markers of oxidative damage. Only one study found an increase in lipid peroxidation for vigorous exercisers (Diaba-Nuhoho et al., 2018). However, the study compared active with inactive individuals and therefore had high variability in training protocols and intensities. Nevertheless, they found several other positive effects of physical activity on overall health. Bobeuf et al. (2011) did not find any significant positive effects in a study that compared four groups: placebo control, vitamin C/E supplementation, RT, and combined RT and vitamin supplementation. However, the average sample size per group was only 14 participants and, consequently, the analysis had low statistical power. In addition, there was no increase in markers of oxidative damage.

The results of the RT interventions point towards positive effects of RT on the redox system: RT fosters healthy redox homeostasis, increases antioxidant capacity, and thus prevents oxidative damage and its negative consequences for health. For possible large-scale interventions, it is important to note, that the effects were consistently observed over a large variety of intervention durations between six weeks and six months, however, the effectiveness of shorter interventions cannot be guaranteed. Further, all intervention programs scheduled time for recovery and limit training to two to three times a week, which facilitates training

adaptations and prevents the detrimental effects of excessive oxidative stress (Winett & Carpinelli, 2001).

The effects mentioned above were only observed in the most widely used redox markers, namely SOD and MDA. All studies used additional markers (TNF-α, uric acid, CAT, GPx, GSH). For those markers, there was either no effect or the effect was in the same direction as the effects on the markers mentioned above. It can be concluded that RT leads to an improvement in redox balance, namely a decrease in oxidants and an increase in antioxidants. However, these training adaptations are either specific for certain antioxidants and oxidants or the effects are general but only measurable on the most prominent markers.

Effects of resistance training on different population groups

Four of the eleven studies examined the effect of RT on older adults (>54 years). Alikhani and Sheikholeslami-Vatani (2019) compared the effect of a 12-week RT protocol at 75% 1RM on younger (18-25 years) and older (55-65 years) women. They found that the antioxidant defense system is strengthened equally for both younger and older women. Bloomer et al. (2008) investigated the effects of an eight-week RT program on older adults (>54 years) with Parkinson's disease. The training was well tolerated, increased antioxidants (SOD, GPx), and decreased oxidative damage (H_2O_2, MDA). These adaptations might counteract the increase of oxidative stress caused by Parkinson's disease. Two studies (Vezzoli et al., 2019; Vincent et al., 2006)

examined the effects of RT on obese, overweight, and sarcopenic older adults (>60 years) and found that long-term exercise reduced exercise-induced oxidative stress. In addition, RT served as a protection against cardiovascular risk factors. The improvements in the antioxidant defense system were correlated with an increase in strength and a reduction in body fat (Cakir- Atabek 2015). This suggests that redox adaptations are part of the overall training adaptations to regular RT. Training effects like a change in body composition are more easily observable than changes in the cellular redox system. A correlation between the two allows easier and cheaper monitoring of all RT adaptations, which can be useful for large-scale RT interventions. The eleven studies were performed on a highly diverse subject pool in different countries with different ethnicities, ages, genders, and health statuses, yet all came to the same conclusion. This confirms the potential for RT interventions to be used as a health intervention for healthy as well as diseased people of all ages and backgrounds.

Comparing the effects of resistance training intensities

Research into RT has shown that there is an intensity threshold below which no or only neglectable training adaptations take place, concerning muscle mass, strength, body composition, and cardiovascular fitness (Winett & Carpinelli, 2001). Studies into exercise-induced oxidative stress suggest a similar threshold for the increase in oxidative stress. At moderate levels, increased ROS enable cellular signaling and immune defense; at high levels, ROS can lead to oxidative damage (Finaud et al., 2006; Hendrix et al., 2020; Powers et

al., 2020; Powers & Jackson, 2008; Thirupathi et al., 2021). The threshold for non-redox adaptations is around 40-50% of either VO2max or 1RM. The experimental studies reviewed here used exercise intensities of 50-90% of (estimated) 1RM, thus all studies were above the threshold where training adaptations should take place. Two studies directly compared the effects of RT at different intensities. Azizbeigi (2015) found that an increase in antioxidant enzymes and a decrease in inflammatory markers following RT are independent of exercise intensity (85-90% of 1RM vs. 65-70% of 1RM). Similar results were observed by Cakir-atabek (2010), who compared strength (85% of 1RM) with hypertrophy (70% of 1RM) training. Both protocols significantly decreased MDA levels and increased GSH. Other studies found a general dose-response relationship between RT and positive health as well as strength outcomes (Blair et al., 2001; Crespo et al., 2002; Winett & Carpinelli, 2001). At very high intensities, the dose-response function is reported to be either asymptotic (Blair et al., 2001) or declining (Powers et al., 2020; Powers & Jackson, 2008; Thirupathi et al., 2021). The latter hormesis function suggests that increased exercise intensity also increases oxidative stress, and therefore, training adaptations up to a certain maximum of exercise-limiting fatigue. Training at intensities beyond the threshold for training adaptations does not lead to greater benefits but instead undermines recovery and causes greater muscle fatigue, overtraining syndrome, and oxidative damage (Powers & Jackson, 2008; Winett & Carpinelli, 2001). Nevertheless, the studies reviewed here did not find negative effects for higher intensities, suggesting that this maximum point is not reached during regular and supervised training conditions with

sufficient recovery intervals. Furthermore, the adaptive effects were found across the whole intensity spectrum from 50% to 90% of 1RM, which again confirms the high variability of effective RT protocols. All those intensities were above the hypothesized threshold for training adaptations. Thus, it cannot be concluded whether there is an intensity threshold for redox adaptations following RT.

DISCUSSION

This review examined the potential benefits of RT of different intensities on redox homeostasis in humans of different ages, gender, and health status. To investigate that research question, eleven studies were compared. Nine of those studies performed RT interventions on previously untrained subjects (Alikhani & Sheikholeslami-Vatani, 2019; Azizbeigi et al., 2013, 2015; Bloomer et al., 2008; Bobeuf et al., 2011; Cakir-atabek et al., 2010; Cook et al., 2013; Vezzoli et al., 2019; Vincent et al., 2006). The remaining two studies compared regular exercisers with non-exercisers (Cakir-atabek & Ozdemir, 2015; Diaba-Nuhoho et al., 2018). The study pool included a wide range of participant backgrounds, intervention durations, and RT intensities. Overall, the findings are positive: consistent RT increases the body's ability to cope with oxidative stress by inducing training adaptations of the redox system. In addition, no negative effects – namely increased oxidative damage – have been found, even though exercise has been proven to induce oxidative stress.

Studies and reviews comparing regular exercisers with inactive people consistently show that an active lifestyle, also involving RT, is related to an increase in the antioxidant defense system (Belviranli & Gökbel, 2006; Cakir-atabek & Ozdemir, 2015; Diaba-Nuhoho et al., 2018), and an overall decrease in risk factors for diabetes, heart disease, cancer, and all-cause mortality (Blair et al., 2001; Crespo et al., 2002; Hendrix et al., 2020; Kraemer et al., 2002; Oguma et al., 2002; Penedo & Dahn, 2005; Powers et al., 2020; Westcott, 2012). However, it has been established oxidative stress is increased during and immediately after exercise. Nevertheless, more recent research suggests that the overall positive health benefits of physical exercise might be linked to the increased ROS production, since ROS aid cell signaling, immune function, and enzyme activation (Belviranli & Gökbel, 2006; Powers et al., 2020; Valko et al., 2007). In addition, the primary exercise-induced oxidative stress might be necessary for the training adaptations. Consequently, if there is an adequate balance between oxidants and antioxidants – redox homeostasis – oxidative damage can be prevented while still allowing for training adaptations. Almost all the studies investigated here show that RT promotes healthy redox homeostasis, the capacity of the body to react sufficiently to short-term increases in oxidative stress and prevents oxidative damage. This also enables the body to prevent diseases related to chronic oxidative stress, or cope better with such diseases (Blair et al., 2001; Bloomer et al., 2008; Hendrix et al., 2020; Westcott, 2012; Winett & Carpinelli, 2001). Still, RT intensity might be an important factor to consider since other research suggested harmful effects of very high-intensity RT (Powers et al., 2020; Winett & Carpinelli, 2001). However, the wide

range of intensities covered in this review, also representing all commonly used intensities, did not suggest a threshold in this normal range. Furthermore, all interventions lasted for a sufficient amount of time for training adaptations to take place. Even though the length of the interventions varied considerably between six weeks and six months, they did not differ in their effects, which supports the efficiency of RT. The training schedules all allowed enough time for recovery, which possibly contributed to the fact that no increase in oxidative damage was found since the body had enough time to recover from exercise-induced oxidative stress. Also, training two-to-three times a week seems to be enough to induce training adaptations.

The reviewed studies all point towards the overall positive health effects of RT as well as training adaptations of the redox system. The findings are in line with the overall preventive and therapeutic health benefits of physical exercise found in other studies (Crespo et al., 2002; Westcott, 2012; Winett & Carpinelli, 2001), however, the mechanisms that lead to the redox adaptations still need to be investigated. In addition, the positive effects mentioned above were observed consistently over age, gender, health status, and training intensity, demonstrating that RT is safe for all kinds of people. It is efficient and effective (Westcott, 2012; Winett & Carpinelli, 2001). Therefore, RT is suitable for large-scale preventive health interventions for the general population. In addition, RT could supplement drug therapy for many common diseases. RT has also been shown to have positive effects on neurodegenerative diseases and mental disorders (Penedo & Dahn, 2005; Raza et al., 2016), therefore possibly also contributing to better brain and mental health. These

findings further expand the range of possible applications of RT interventions.

This review has several limitations. Firstly, it is based only on a small number of empirical studies. In addition, it is subject to the limitations of the individual studies, such as the small sample sizes per group, the lack of longitudinal studies or later follow-ups, and the correlational and often insignificant evidence. Another limitation is the individual differences in nutrition - diet was sometimes matched and documented but never manipulated. Additional limitations arise from comparing the studies. The studies used highly diverse subject pools as well as a variety of markers for antioxidants, oxidative stress, and oxidative damage which make it harder to compare the results, especially since particular markers (SOD, MDA) seem to react more reliably to RT than others (GSH, TAC, TNF-α). Yet, it can be seen as evidence for our conclusion that, despite the diversity in the compared studies, the positive effect could be consistently reported.

Future research should manipulate diet as a possible confounding factor and compare intensities over a wider spectrum to learn more about the dose-response relationship between RT and health. Longitudinal studies or later follow-ups should also be performed. To increase the comparability of studies, it would be helpful to have a standard of markers used to assess oxidative stress and damage as well as antioxidant capacity. Lastly, the mechanisms underlying the training adaptations of the redox systems should be investigated for a better understanding of the factors contributing to positive and possible negative effects.

To conclude, RT should be recommended as preventive and therapeutic health behavior to increase physical and mental health in the whole population. It is safe for all ages, genders, and personal backgrounds. Still, it is recommended to consult an expert to construct a training program that is adapted to individual characteristics and based on science to achieve optimal results.

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This paper is the product of students from the Faculty of Psychology and Neuroscience, Maastricht University and is meant for student educational purposes only.

KIM CARINA HOFFMANN

NMDAR-dependent LTP versus LTD induction: The role of Ca2+ influx amplitude

Literature Review

Long-term potentiation (LTP) and long-term depression (LTD) are two types of synaptic plasticity thought to be involved in learning and memory. Specifically, LTP refers to the strengthening of synapses while LTD refers to the weakening of synapses. Interestingly, both N-methyl-D-aspartate receptor-dependent LTP and LTD are induced by a calcium influx into the post-synaptic cell. This raises the question of how the cell selectively induces either LTP or LTD. Early research suggested the amplitude of calcium influx as a decisive mechanism. The essay critically evaluates this hypothesis by reviewing evidence and alternative candidates, namely the timing and location of calcium influx, N-methyl-D-aspartate receptor subunits, and the competition between α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor exocytosis and endocytosis. The essay concludes that the amplitude of calcium influx should be seen as only one of

multiple components entailed in the complex decisive machinery for selective LTP versus LTD induction.

Keywords: neuroplasticity, long-term potentiation, long-term depression, calcium, NMDA receptors

INTRODUCTION

NMDAR-dependent LTP versus LTD induction: The role of Ca2+ influx amplitude

Synaptic plasticity, meaning activity-dependent changes in efficacy and strength of neuronal connections, is thought to underly learning and memory (Magee & Grienberger, 2020). Two types of synaptic plasticity are long-term potentiation (LTP) and long-term depression (LTD). Specifically, the former refers to the strengthening of synapses, while the latter refers to the weakening of synapses (Pinar et al., 2017). The most prominent form of LTP and LTD in the central nervous system is N-methyl-D-aspartate receptor (NMDAR)-dependent, but there exist other NMDAR-independent forms of synaptic plasticity (e.g., glutamate metabotropic receptor-dependent LTP; Alkadhi, 2021). Interestingly, NMDAR-dependent LTP and LTD are both induced by the influx of calcium (Ca2+) into the post-synaptic cell. Thus, the question arises how the cell selectively chooses between LTP and LTD (Lüscher & Malenka, 2012; Alkadhi, 2021).

The post-synaptic membrane contains NMDARs and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs). Both receptor types are ligand-gated ion channels that are activated by glutamate (Lüscher & Malenka, 2012). Upon glutamate binding, AMPARs allow the large influx of sodium (Na2+) with a simultaneous small efflux of potassium (K+) ions leading to the depolarization of the post-synapse (Chater & Goda, 2014). In contrast, activating NMDARs requires the binding of glutamate and the depolarization of the post-

synapse. Only if both requirements are met, a magnesium (Mg2+) ion is pulled outside the NMDAR pore, allowing the influx of Ca2+. Upon Ca2+ influx, kinases and phosphatases are activated which insert or remove synaptic AMPARs respectively, thereby, altering synaptic sensitivity in opposite directions (Malenka & Bear, 2004; Bartlett et al., 2007; Lüscher & Malenka, 2012).

As both types of NMDAR-dependent synaptic plasticity can be induced by Ca2+ influx, the cell must have a decisive mechanism to selectively induce LTP or LTD. Artola and Singer (1993) developed the differential threshold hypothesis, postulating that it is the amount of Ca2+ entering the post-synaptic cell that selectively induces LTP or LTD. Specifically, LTP in hippocampal cells can be experimentally induced by high-frequency stimulation (1s train at 100Hz) that causes a great rise in Ca2+, while LTD is induced by low-frequency stimulation (600-900 pulses at 1-5Hz), causing a lower rise in Ca2+ (Raymond, 2007; Massey & Bashir, 2007). Based on the differential threshold hypothesis, this essay critically evaluates whether the amount of Ca2+ influx can be seen as a decisive mechanism for selectively inducing NMDAR-dependent LTP or LTD.

Starting at the top – Amplitude, duration, location

The differential threshold hypothesis was supported by several blocking studies. As activating kinases requires a large Ca2+ influx and activating phosphatases requires a moderate Ca2+ influx, the idea was to block either of the two to investigate the subsequent effects on LTP and LTD induction, respectively. Specifically, inhibiting calcium-calmodulin kinase II (CaMKII) blocked LTP, while protein phosphatase inhibitors blocked LTD (Artola & Singer, 1993; Lisman,

1989). However, the Ca2+ influx is not only characterised by its amplitude, but also by its duration and its location (Evans & Blackwell, 2015). By experimentally manipulating the amplitude of Ca2+ influx (e.g., by omitting the Mg2+ ion from the NMDAR pore or blocking NMDARs and/or AMPARs), a study revealed that the duration of stimulation is critical to induce either LTP or LTD (Mizuno et al., 2001). Several studies confirmed that LTP induction requires strong, brief stimuli, while LTD induction requires moderate, prolonged stimuli (e.g., Yang et al., 1999). Moreover, research suggests that the specific site of Ca2+ entry determines targets to which Ca2+ will bind and subsequently induces either LTP or LTD (Evans & Blackwell, 2015). For example, one study showed that activation of synaptic NMDARs induces LTP, while activation of extrasynaptic NDMARs induces LTD (Liu et al., 2013).

Taken together, numerous studies provided evidence in favour of post-synaptic Ca2+ influx being the decisive mechanism underlying selective LTP and LTD induction. However, LTP and LTD induction cannot be explained by the amplitude of the Ca2+ influx alone, but rather by a combination of the amplitude, duration, and location of the Ca2+ influx. Therefore, the differential threshold hypothesis should be complemented by a temporal and a spatial factor to increase its explanatory power (Evans & Blackwell, 2015). Even though, this conclusion is reasonable and in line with research findings, Ca2+ influx characteristics only pose a decisive candidate for inducing NMDAR-dependent LTP or LTD at the beginning of the synaptic plasticity cascade. Additionally, alternative candidates at later stages of the cascade should be considered.

Going one step further - NMDAR subunits

An alternative hypothesis suggests that it is the constellation of NMDAR subunits that selectively induces LTP or LTD, as NMDAR subunits confer different gating and pharmacological properties (Kash & Winder, 2007). NMDARs consist of two N1 and two N2 subunits. The constellation of N2 subunits can vary, as there are four subtypes (i.e., N2A, N2B, N2C, N2B) (Lüscher & Malenka, 2012). Support for the differential involvement of N2 subunits in LTP and LTD in hippocampal CA1 synapses of adult rats comes from Liu and colleagues (2004). They showed that administering a N2A antagonist (NVP-AAM077) resulted in the absence of LTP, while administering N2B antagonists (ifenprodil and R025-6981) prevented the induction of LTD (Liu et al., 2004). Similar findings were obtained for amygdalae NMDAR subunits in adult rats (Dalton et al., 2012).

However, there are contradictory findings. For example, a study has shown that administering a N2A antagonist (NVP-AAM077) inhibited LTD as well as LTP induction in hippocampal slices of two-week old rats (Bartlett et al., 2007). Additionally, this study found no effect of administering a N2B antagonist (R025-6981) on LTD, but on LTP induction (Bartlett et al., 2007). Even though, these contradictory findings might be explained by confounding factors (e.g., developmental stage, antagonist concentration, multiple drug targets), it becomes apparent that no definite conclusion can be drawn regarding the role of NR2A and NR2B subunits in selectively inducing LTP and LTD (Kash & Winder, 2007). Additionally, only few studies have investigated the potential role of the N2C or N2D subunits. Bartlett and colleagues (2007) highlighted that the N2A antagonist

NVP-AAM077 may have had additional inhibitory effects on N2C and N2D subunits, but further research is needed. In sum, research has not found distinct roles of NMDAR subunits in synaptic plasticity (yet). Therefore, they cannot (yet) be seen as a decisive mechanism for selectively inducing LTP or LTD. However, the synaptic plasticity cascade involves multiple other downstream candidates.

Going all in - Downstream mechanisms

It is widely accepted that the expression of LTP and LTD requires the insertion and removal of AMPARs from the post-synaptic membrane, respectively (Park, 2018). Specifically, post-synaptic AMPAR insertion is induced by the initial Ca2+ influx that activates kinases (e.g., CaMKII) that phosphorylates proteins. The exocytosis of AMPARs is mediated by the Ca2+ sensor synaptotagmin-1 (Syt1). In contrast, AMPAR removal is induced by Ca2+ influx activating phosphatases (e.g., calcineurin, protein phosphatase 1) which leads to dephosphorylation of proteins. The endocytosis of AMPARs is mediated by the Ca2+ sensor Protein Interacting with C Kinase 1 (PICK1) (Lüscher & Malenko, 2012; Chater & Goda, 2014). A recent study proposes the competition between endocytosis and exocytosis of AMPARs as the decisive mechanism underlying selective LTP versus LTD induction (Sumi & Harada, 2020).

Sumi and Harada (2020) built a network model to reproduce the bidirectional synaptic plasticity in hippocampal neurons. In their final model, endo- and exocytosis of AMPARs are induced to differential extents, depending on whether PICK1 or Syt1 is activated

by the stimulation protocol. Interestingly, PICK1 (driving endocytosis) is activated by both LTP (i.e., strong and brief high-frequency) stimulation and LTD (i.e., moderate and prolonged low-frequency) stimulation, while Syt1 (driving exocytosis) is activated mainly by LTP stimulation. Consequently, LTP stimulation activates both PICK1 and Syt1 leading to a competition between insertion and removal forces on AMPAR trafficking. However, as LTP stimulation creates a greater maximum exocytic drive than maximum endocytic drive, AMPAR exocytosis wins the competition and LTP is expressed. In contrast, LTD stimulation activates mainly PICK1, leading to a greater endocytic than exocytic drive. Thus, AMPARs are removed from the post-synaptic membrane, leading to LTD expression (Sumi & Harada, 2020).

The hypothesis by Sumi and Harada (2020) poses an interesting candidate for the selective induction of NMDAR-dependent LTP versus LTD. The model takes NMDAR-dependent Ca2+ influx as the input for LTP and LTD, which is in line with early hypotheses about the critical role of Ca2+ influx characteristics, namely its amplitude, duration, and location. Additionally, the model incorporates recent knowledge about downstream signalling pathways of LTP and LTD including (de)phosphorylation of proteins, AMPAR trafficking dynamics, Ca2+ sensors, and the recycling endosome. Lastly, it proposes a competition mechanism that allows for hypotheses that can be validated or refuted by future research (Sumi & Harada, 2020). However, research already examines other potential candidates and their roles in selectively inducing NMDAR-

dependent LTP versus LTD (e.g., CaMKII holoenzyme; Cook et al., 2021).

CONCLUSION

Even though, more research is needed to investigate the selective mechanism underlying LTP and LTD induction, this essay argues in favour of a complex decisive machinery that entails multiple processes at different levels of the synaptic plasticity cascade. However, this essay is subject to several limitations. Selected research focused on NMDAR-dependent LTP and LTD occurring at excitatory synapses only. However, the picture is more complex, involving synaptic plasticity at inhibitory synapses, NMDAR-independent plasticity forms, and different mechanisms depending on cell types, brain regions, and the developmental state. Despite these limitations, several conclusions can be drawn regarding the role of Ca2+ influx amplitude in selectively inducing NMDAR-dependent LTP or LTD.

The search after a decisive mechanism for the selective induction of NMDAR-dependent LTP and LTD has yielded no comprehensive machinery yet. Early research proposed Ca2+ influx characteristics during induction, namely its amplitude, duration, and location, as potential candidates. However, it is reasonable that a decisive mechanism for bidirectional synaptic plasticity does not only consider characteristics present during the induction phase, but that it also includes components of later stages. While there are no conclusive results for the involvement of different NR2 subunits in the decisive

machinery, a recent network model proposes the competition between AMPAR exocytosis and endocytosis to be involved in the selective induction of LTP versus LTD. However, future research needs to validate and test the suggested neural network model. Taken together, Ca^{2+} influx amplitude should be seen as one of multiple components entailed in the complex decisive machinery for selectively inducing NMDAR-dependent LTP and LTD.

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LOU ANTOINETTE GODVLIET

Not New, but Nearly Forgotten: Hypnodelic Therapy as Treatment for Addiction

Literature Review

Hypnosis and psychedelics have long been used as adjuncts to psychotherapy for the treatment of various psychiatric disorders such as addiction. However, only a few patients respond to either hypnotherapy or psychedelic-assisted psychotherapy. Therefore, combining them (= "hypnodelic" therapy) might be beneficial for therapeutic outcomes. This review provides an outline of studies in which hypnosis and LSD were combined with psychotherapy in patients with drug addiction. Hypnodelic therapy has been found to produce significantly greater improvement in depression and anxiety of narcotic drug patients compared to other combinations of these treatment techniques. Additionally, hypnodelic therapy is suggested to produce the greatest alteration of consciousness. Possible mechanisms of action will be discussed. It is concluded that hypnodelic therapy deserves renewed scientific interest because it represents a promising treatment technique for patients with drug addiction.

Keywords: addiction; hypnodelic therapy; LSD; hypnosis; consciousness

INTRODUCTION

A century ago, it was recognized that patients with drug addiction are in desperate need of improved treatment. The efficacy of psychiatric treatments during that time (e.g., individual and group psychotherapy) was considered insufficient. Patients demonstrated a lack of motivation and their attendance at therapy sessions was unreliable. In fact, high discharge rates against-medical-advice were common (Ludwig & Levine, 1967, p.130).

Moreover, the large number of patients to be treated and the unsuccessful results of follow-up studies investigating the discharged patients, highlights the need for more effective treatment techniques (p.131).

Drug addiction or dependency develops after repeated substance use and includes several behavioural, cognitive as well as psychophysiological phenomena. A strong desire for the drug and loss of control lead to persistent use without acknowledging the harmful effects and neglect of other interests (World Health Organization, 2004). Neurologically, addiction is characterised by abnormal functioning of the default mode network (DMN) and disturbed interaction between the DMN and other large-scale networks (Zhang & Volkow, 2019). The high comorbidity of substance use disorders (SUD) and posttraumatic stress disorder (PTSD) ranging from 30 to 59 percent (Stewart et al., 2000) suggests that exposure to traumatic events can contribute to drug addiction. According to the self-medication hypothesis by Chilcoat and Breslau (1998), individuals

with PTSD believe that the substance use will relieve them from their symptoms. These PTSD-related symptoms might, in turn, represent a trigger of relapse (Norman et al.,2007).

Recovery from addiction is a multi-dimensional process. The motivation to change, self-efficacy, and social support are only some of the mechanisms promoting recovery (Bogenschutz & Pommy, 2012). Achieving altered states of consciousness might represent a basic human motive. As many addiction patients use these substances destructively to achieve altered states of consciousness (McPeake et al., 1991), treatments should offer alternative and less harmful means for this purpose. A failure to address this need of patients could negatively impact their motivation to change as well as increase craving and subsequently contribute to relapse. According to the "stage" model of addictions by Prochaska, DiClemente, and Norcross (1992), there are five stages of change. Precontemplation and contemplation require mainly cognitive processes. Following the preparation, action and maintenance are acquired by changing behavioural processes (Prochaska et al., 1992). Hence, it is important that treatments for addiction address cognitive, behavioural, and psychological processes that are involved in the recovery process.

Studies on psychedelic compounds such as lysergic acid diethylamide (LSD) demonstrate their clinical potential for patients with drug addiction by mobilizing biological and psychological processes (Bogenschutz & Pommy, 2012). LSD has been found to be effective for the treatment of alcoholism and opioid addiction (Krebs & Johansen, 2012; Ludwig & Levine, 1965). Psychedelic induced mystical experiences can trigger sudden and lasting behavioural

changes. Some studies indicate that this new state of consciousness or spiritual awakening might be a predictor of abstinence. Hallucinogens may also be able to increase motivation as well as self-efficacy and reduce craving (Bogenschutz & Pommy, 2012). Considering that reaching an alternate state of consciousness is part of the addictive process and most treatments lack alternatives to address this need of patients potentially increasing the risk of relapse (McPeake et al., 1991), psychedelics demonstrate great therapeutic potential in this field.

In the 1960s, it quickly became clear that this new approach of psychedelic treatment demanded for further research with bigger sample sizes but also techniques, such as hypnosis, that would enhance its therapeutic efficacy. Ludwig and Levine (1967) believed that it is important to control the LSD experience. More specifically, the aim is to channel the therapeutic potential of the psychedelic experience in order to maximize the probability of its therapeutic success. Notably, the perception altering qualities (e.g., temporal perception) of the drug were not held solely responsible for its therapeutic success and, thus, might only exert an indirect influence on the latter (Ludwig & Levine, 1967).

Various studies suggest the use of hypnosis to be potentially advantageous in modifying and structuring psychedelic experiences (Lemercier & Terhune, 2018; Oakley & Halligan, 2009; Gubel, 1962). The hallucinogenic and hypnotic experiences demonstrate some similarities such as an increase in introspection and experiences of depersonalizations (Gubel, 1962). Additionally, hypnotic suggestion has been found to be a powerful cognitive tool of hypnosis that can be

used to explore certain phenomena which are relevant to cognitive and clinical neuroscience (Oakley & Halligan, 2009). For instance, hypnotic suggestion can be used to study the responses to psychedelic drugs in a controlled fashion which might enhance their therapeutic efficacy (Lemercier & Terhune, 2018). Therefore, the combination of LSD and hypnosis seems promising not only in a psychotherapeutic setting but also with regards to fundamental research of human consciousness.

The term 'hypnodelic' is a blend of 'hypnotic' and 'psychedelic' which describes the states of consciousness evoked by the corresponding methods (i.e., hypnosis and acute psychedelic drug administration). Hypnodelic therapy is defined as the combination of psychedelic drugs, hypnosis, and psychotherapy. This review focusses on LSD as a psychedelic drug because the original studies from Ludwig and Levine (1965-1967) exclusively applied this drug probably due to its powerful anecdotes (Wesson, 2011) and remarkable potency (Johnson, 2018). Throughout this review, the term hypnodelic therapy will, therefore, refer to the combination of LSD, hypnosis, and psychotherapy.

Although psychedelics and hypnosis show multiple phenomenological parallels, the literature is scarce and most research on these topics has been carried out in isolation (Lemercier & Terhune, 2018). Both hypnosis and psychedelics remain controversial subjects. The "war on drugs" and the associated highly negative reputation of psychedelic substances displayed by the media as well as the criminalization led to the prohibition of many psychedelic substances during the mid-1960s. This, in turn, limits the availability

of scientific studies and literature on these treatments drastically (Dyck, 2005).

This review consists of three main parts. Namely, hypnotherapy, psychedelic therapy, and finally, hypnodelic therapy. The current review begins by examining hypnotherapy (the combination of hypnosis and psychotherapy), its use in the past, and its reported efficacy. It will then go on to the past findings regarding the adjunct use of LSD in a psychotherapeutic setting and its efficacy. By discussing the current state of research in terms of hypnosis and LSD as adjunct to psychotherapy individually, it should become apparent whether the combination of those treatment techniques has an additive value or not. In case of the latter, it is possible that both treatment techniques cancel each other's effectiveness out, are independent of one another or show a disadvantageous effect that would need further research and is beyond the scope of this review. The third part draws upon the entire review by evaluating studies of hypnodelic therapy, tying up the various theoretical and empirical strands. A discussion with limitations and implications of the findings for the psychotherapeutic treatment of drug addiction follows. Moreover, areas for further research are identified. Finally, the conclusion gives a concise summary and critique of the reviewed findings.

This review will examine the studies investigating the efficacy of treatment techniques involving LSD, hypnosis, and psychotherapy. In particular, it seeks to address the following question: Can hypnosis increase the efficacy of LSD utilization in psychotherapy for patients with drug addiction? On the one hand, critically reviewing past

research may be the first step towards an approved treatment technique with potentially high therapeutic efficacy. On the other hand, the conclusion might offer new insights into each of the treatment techniques individually and whether their combination could be beneficial for therapeutic outcomes.

Hypnotherapy

In general, hypnosis is described as a state of consciousness that involves not only focused attention but also reduced peripheral awareness achieved by the power of suggestion (American Society of Clinical Hypnosis). Suggestions can be defined as a request to experience an imaginary situation pretending for it to be real (Lynn et al., 2015). Clinical hypnosis is a mind-body intervention (Lemercier & Terhune, 2018) that is able to change physiological along with psychological functions of a patient in different ways. For instance, mental imagery and suggestions may complement the impact of presented ideas on the mind. Additionally, unconscious exploration during hypnosis can assist the understanding of motivations, experiences, and emotions (American Society of Clinical Hypnosis). Overall, hypnosis implements improvements in affect, cognition, and perception (Lemercier & Terhune, 2018) related to various psychopathologies such as depression and eating disorders (Alladin, 2010; Barabasz, 2007)

A standard session of clinical hypnosis normally consists of three phases of suggestions. Firstly, the induction is initiated by using suggestions for an enhanced absorption of the spoken words and

reduced metacognition. Further suggestions are given in the second phase to modulate the contents of consciousness. Finally, the deduction phase applies suggestions to restore normal alertness. Posthypnotic suggestions can be applied if recommended (Barnier & McConkey, 2014). Typically, patients feel a lack of authorship over the response to suggestions. This finding has been measured by self-reports as well as implicit perceptual indices. Hypnotic suggestibility is measured by well-validated behavioural scales and has been found to be normally distributed, stable over long periods of time, and to be at least somewhat hereditary (Piccione et al., 1989; Morgan et al., 1970).

In a clinical setting, hypnosis aims at stimulating emotional catharsis as well as beneficial changes in self-image, perceptions, behaviour (e.g., habits), and general health. Individual differences in certain factors such as the responses to hypnotic suggestibility are likely to affect the desired results. However, the association between the efficacy of hypnosis and hypnotic suggestibility was found to be weak due to a variety of non-hypnotic factors, such as the motivation and expectancies of the patient. Therefore, the responsiveness to hypnotic suggestions is not exclusively influenced by hypnotic factors (Montgomery et al., 2011; Lynn et al., 2008). Considering that suggestibility does not seem to influence the therapeutic outcome, hypnotherapy can be applied to a large group of patients.

Responses to hypnotic suggestions have certain neurophysiological correlates which are impaired in patients with drug addiction. Chronic alcohol addicts demonstrate a disruption of the dopamine receptor activity as well as cognitive functions in the

anterior medial prefrontal cortex (amPFC; Trantham-Davidson et al., 2014) In general, the mPFC contributes to the Theory of Mind (ToM, i.e., being able to consider the beliefs and intentions of others; Geng et al., 2017). Impairments of this function have been found in cocaine-dependent users but not in drug-naives (Sanvicente-Vieira et al., 2017). The amPFC is also part of the Default-Mode Network (DMN) involved in attention as well as functions of the ego such as reality testing (Carhart-Harris et al., 2015). This so-called resting state is characterised by low frequency oscillations and displays abnormal functional connectivity in heroin addicts. This abnormal functioning, in turn, results in a diminished cognitive control that may explain the hypersensitivity to drug related cues (Ma et al., 2011). Several experimental studies have investigated the activity of the DMN and found that it was reduced during hypnosis. More specifically, activity in the anterior parts of the DMN in highly suggestible people might reflect non-goal-directed cognitive activity or a so-called "state of readiness" in order to respond to subsequent suggestions (McGeown et al., 2009). Additionally, the global functional connectivity between the insula and dorsolateral prefrontal cortex (DLPFC) is higher under hypnotic suggestions and indicates reduced metacognition (Cardeña et al., 2013). The insula shows increased dopamine levels during drug intoxication and the DLPFC is more active in response to salient drug cues (Jasinska et al., 2014). However, the association between metacognitive beliefs and addictive behaviours is in need of further research (Spada et al., 2015). Remarkably, hypnosis has been found to influence brain plasticity positively (Halsband et al., 2009). This, in turn, can contribute to the reversion of a previously established

sensitisation to cocaine (Chen et al., 2008). Altogether, these neurophysiological effects following hypnosis might explain its therapeutic potential for patients with drug addiction on a neurophysiological basis.

Hypnosis is generally considered safe and an effective adjunct to psychotherapy. A systematic review of meta-analyses of randomized controlled trials studying medical hypnosis found no significantly higher rates of adverse effects resulting from hypnosis compared to control groups (Häuser et al., 2016). Hypnosis has been applied to an assortment of physical conditions (e.g., chronic pain and post-menopausal hot flashes) and likewise psychological conditions (e.g., anxiety and depression), but has also been proven to be particularly successful in the treatment of addictions such as nicotine, alcohol, and barbiturates (Hartman, 1972; Katz, 1980). Critically, success rates of conventional programs (i.e., short-range programs) for patients with drug addiction have been around two percent, whereas programs employing hypnosis noted success rates between 60 and 70 percent (Hartman, 1972). Thus, hypnosis is considered a relatively safe and efficacious intervention to amplify therapeutic outcomes for patients seeking treatment with psychopathological and somatic symptoms (Bollinger, 2018; Lemercier & Terhune, 2018). Interestingly, not only hypnosis but also LSD has been shown to be an effective adjunct to psychotherapy.

Psychedelic Therapy

Lysergic acid diethylamide (LSD) – also known as "yellow sunshine" or "acid" – has been popular among recreational users since it's discovery because of the mind-altering effects and visual hallucinations it can induce. The most potent hallucinogenic drug (Nichols, 2004) is semisynthetic as it is derived from an ergot (Passie et al., 2008). LSD mainly targets the serotonin 2A receptors (5-HT2A) and, hence, belongs to the classic psychedelics (González-Maeso et al., 2007). In contrast, all addictive drugs such as amphetamines, cocaine and opiates increase extracellular levels of dopamine in the mesoaccumbens pathway which produces dependence or addictive symptomes. Thus, serotonergic hallucinogens are considered non-addictive as they lack the sufficient pharmacological properties to initiate or maintain dependence (Ross, 2012). LSD is not neurotoxic and generally well tolerated (Passie et al., 2008). Universally, LSD produces an array of effects that last from eight to 12 hours (Johnson, 2018). Dependent on the route of administration (e.g., using blotter paper or eyedrops), it takes 40 to 90 minutes for the drug to produce its psychoactive effects. The experience itself is mainly described by users as feeling a sense of openness, heightened emotional sensitivity, vivid colour perception, an altered sense of time and borders "bleeding into each other".

The subjective effects of psychedelics could be beneficial for therapeutic outcomes. Non-linear thought patterns and honest self-analysis which is still compassionate are common during psychedelic experiences (Johnson, 2018). LSD allows its consumers to see old ideas

in a new light and accept these more readily (Ludwig & Levine, 1965, p.432). Additionally, LSD strengthens the relationship between patient and therapist which is very important for the therapeutic outcome as the patient needs to feel safe in order to fully give into the psychedelic experience. The altered perception of time under the influence of LSD makes it easier for the patient to understand connections between his or her present feelings and behaviours as well as traumatic incidents of the past (p.433). LSD is also known for its ability to produce a mental state in which meaning and significance of both thoughts and feelings are enhanced (p. 432). These deeply personal and spiritually meaningful experiences are defined as "mystical-type experiences" which have been associated with continuous positive effects on psychological well-being as well as personality. Mystical-type experiences also influence the nature and quality of the patients' response which in turn significantly determines the therapeutic outcome (Bogenschutz et al., 2015). Noteworthy, mystical-type experiences share certain characteristics with other mystical experiences that are non-drug-related. These include, for instance, the transcendence of time and space, a sense of sacredness and unity, and persisting positive changes in attitudes as well as behaviour towards oneself, others, and life overall. When the acute effects of the drug subside, the "psychedelic afterglow" starts to exert its effects on the patient. During this period of approximately two weeks to a month, the effectiveness of psychotherapeutic interventions has been shown to be enhanced although longer-lasting effects remain controversial (Majic et al., 2015).

Psychedelics can mobilize psychological processes which could promote recovery from drug addiction if administered in a therapeutic setting. Psychedelic induced personality changes or disruption of conditioned responses could reduce craving. The personality dimensions Agreeableness, Conscientiousness, and Extraversion have been found to be associated with self-efficacy. This belief in one's own ability to successfully execute behaviour (i.e., abstinence) to achieve an outcome (i.e., recovery) is a significant predictor of treatment outcome. Thus, psychedelic induced personality changes might not only reduce cravings but also increase self-efficacy. A psychedelic induced mystical experience might help patients to be more accepting of change and new ideas (Bogenschutz & Pommy, 2012). Psychedelics such as MDMA can also be used for exposure therapy in patients with PTSD as they enable them to revisit the traumatic experience in an emotionally engaged state (Mithoefer et al., 2011) and subsequently reduce the risk of relapse. Motivation to change is another mechanism that promotes recovery from drug addiction. Psychedelics may increase motivation to change through self-efficacy, consciousness raising especially with regards to the negative consequences, or a change in perspective resulting in an enhanced desire to change (Bogenschutz & Pommy, 2012).

Psychedelics can mobilize several biological processes which could promote recovery from drug addiction if administered in a therapeutic setting. Psychedelics may reduce craving by improving mood, normalizing stress, or diminishing anxiety and attentional bias. Addiction patients have impaired inhibitory processes and impulse control. These processes are also associated with serotonin (or a lack

thereof). Hence, substances that increase serotonergic activity in the central nervous system (CNS) could reduce craving and relapse (Wise & Robble, 2020; Bogenschutz & Pommy, 2012). Psychedelics do not only influence mood and impulse control but also alter the activity of neuronal networks (Carhart-Harris et al., 2016).

Abnormal functioning of the DMN is associated with psychopathology and represents a promising target for the treatment of addiction. Hyperactivity and hyperconnectivity of the DMN were found in schizophrenic and depressive patients (Whitfield-Gabrieli & Ford, 2012). Alterations of the DMN have been associated with various aspects of drug addiction. More specifically, aberrant functioning of the DMN as well as disturbed interaction between the DMN and other large-scale networks correlate with increased craving and relapse. They are believed to be at least partially responsible for negative emotions, rumination, and impaired self-awareness in patients with drug addiction (Zhang & Volkow, 2019). Successful behavioural interventions such as cognitive behavioural therapy (CBT) or mindfulness training can reduce drug use by focusing on self-referential processing and influencing DMN activity accordingly (Thayer & Feldstein Ewing, 2016). Thus, the DMN may be a potential biomarker for addiction risk and promising target for therapeutic interventions (Zhang & Volkow, 2019).

Psychedelic states can induce alterations of DMN activity and connectivity. A desynchronization of cortical oscillations across brain regions can be observed during psychedelic states (Muthukumaraswamy et al., 2013). The long-distance communication within the DMN seems to be altered with respect to efficiency and

decreased integrity is observed (Carhart-Harris et al., 2016). Both observations might underlie the therapeutic potential of psychedelics through the stimulation of serotonin receptors (Muthukumaraswamy et al., 2013). The so-called "ego death" or "ego dissolution" is characterized by the disintegration of the perceived "self" (identity) that is miscellaneous from others and the environment (Liechti, 2017). These feelings of ego dissolution are hypothesized to arise from the decoupling of DMN and medial temporal lobe (MTL) regions (Lebedev et al., 2015). Different dimensions of ego dissolution are associated with region-dependent alterations of glutamate levels. More specifically, glutamate levels increased in the mPFC and decreased in the hippocampus of participants who received psilocybin compared to controls. Alterations of glutamate in the mPFC predicted negatively experienced ego dissolution. In contrast, a positively experienced ego dissolution was predicted by alterations of glutamate in the hippocampus (Mason et al., 2020).

The therapeutic potential (i.e., antidepressant and anxiolytic effects) of classic psychedelics such as LSD and Dimethyltryptamine (DMT) is believed to be at least partially generated through the process of enhanced neuronal plasticity. Psychedelics have been found to promote structural neuroplasticity such as neurogenesis, spinogenesis, and synaptogenesis. Additionally, psychedelics induce functional neuroplasticity by increasing the frequency and amplitude of spontaneous excitatory postsynaptic currents (EPSCs) especially in prefrontal cortical neurons. Psychiatric disorders may be considered disorders of neuroplasticity. Impaired neurogenesis is hypothesized to contribute to the pathophysiology of depression as patients with MDD

demonstrate smaller hippocampal volumes. Additionally, there is a noticeable overlap between neuroplasticity and the molecular as well as cellular mechanisms activated by classical antidepressants (Pittenger & Duman, 2004). These increase adult neurogenesis in the hippocampus and block the effects of stress on neurogenesis (Duman, 2004). Different types of neuroplasticity are linked with certain serotonergic proteins. For instance, the 5-HT2A is associated with dendritic and spine morphology as well as synaptic plasticity (Kraus et al., 2017).

Serotonergic hallucinogens are also known to increase brain derived neurotrophic factor (BDNF) transmission. Animal studies have associated this with decreased alcohol self-administration and diminished cocaine-seeking behaviour in the dorsal striatum and medial PFC respectively. The increase in BDNF transmission could mediate glutamate-dependent neuroplastic adaption that normalizes functional connectivity in the prefrontal-limbic circuitry and exert an anti-addictive effect (Ross, 2012).

Non-pharmacological aspects can influence the psychedelic experience and affect safety concerns accordingly. The intention, expectation, and preparation of the patient are considered the “set” while the physical and social environment is called the “setting”. Depending on those two factors, the same drug can elicit very different emotions. For instance, LSD can relieve anxiety, promote joy and cognitive enhancement, but also induce feelings of fear and suspiciousness (Hartogsohn, 2016). If the patient encounters anticipatory anxiety and does not feel safe in his or her environment, a so-called “bad trip” can occur. These negative experiences are mainly

characterized by paranoia and fear of death or going insane and might occur in the same trip as the desirable effects (Johnson, 2018). Notably, during a clinical self-experimentation with LSD, none of the 22 subjects reported any long-term negative effects of the LSD experience. Although the dosages were not controlled for, approximately 90 percent of them described long-term positive effects on different domains such as self-awareness (Winkler & Csémy, 2014). Therefore, psychedelics are considered relatively safe when patients are well-prepared (set) and being used in a supportive environment (setting).

Various studies investigated the effects of LSD in psychedelic-assisted psychotherapy with promising results in the treatment of anxiety disorders (i.e., 77.8% of participants experienced a reduction of anxiety), obsessive-compulsive disorder (OCD), and addictions such as alcohol (Gasser et al., 2015; Zghoul & Blier, 2003; Abramson, 1967;). Therefore, psychedelics might be able to meet an unfulfilled need in the treatment of psychiatric disorders acting as "psychotherapeutic catalysts" (Gubel, 1962). More specifically, a meta-analysis found consistent and significant improvement in 59% of the LSD-treated alcohol addict patients compared to 38% in the control group with a total of 325 subjects across six studies (Bogenschutz & Johnson, 2016). Recently, it seems more important to design an optimal trial for demonstrating efficacy instead of trying to define the "right" patient population (Carhart-Harris & Goodwin, 2017).

So far, it has been reviewed how hypnosis and LSD, each on their own, have the potential to improve therapeutic outcomes.

Therefore, the combination of these two treatment techniques might harbour additional benefits in a clinical setting.

Hypnodelic Therapy

Despite its critics, hypnodelic therapy appeared to be a more potent treatment technique than conventional forms of therapy when research with LSD was still permissible (Ludwig & Levine, 1967). Ludwig and Levine (1967), the founders of the hypnodelic therapy, were eager to test their hypothesis that hypnosis could be used to modify the LSD experience in therapeutically beneficial ways. For a start, they conducted a pilot study including 12 patients with drug addiction which showed promising results. Most of the patients experienced distinct symptom relief, a new outlook on life, and the conviction of remaining abstinent (Ludwig & Levine, 1967).

Thereupon, Ludwig and Levine undertook the first controlled study investigating hypnodelic therapy. For this, 70 patients with drug addiction were randomly assigned to five treatment conditions: hypnodelic therapy (LSD, hypnosis, and psychotherapy), LSD and psychotherapy (psychedelic), psychopharmacological treatment (LSD alone), hypnotherapy (hypnosis and psychotherapy), and psychotherapy (Ludwig & Levine, 1967). Each patient received a single, standardized preparatory session lasting two and a half to three hours. The session consisted of the following two parts. First, a psychiatric information-gathering interview was conducted including chief complaints, past history, self-description, drug history, psychosexual

history, and treatment expectations. Forthwith, the patient was familiarized with hypnosis by the means of a high eye fixation induction technique. Standardized hypnotic challenges were intended to measure the suggestibility of the patient (Ludwig & Levine, 1965).

Hypnodelic Procedure

The authors designed a self-administered questionnaire called the Psychiatric Evaluation Profile (PEP) which consists of 208 items selected on an a priori "clinical" basis (Ludwig & Levine, 1965, p.418). The level of psychopathology exhibited by an individual at a given time was assessed on 11 scales. Eight scales measured psychopathology (e.g., Anxiety, Depression, Paranoid Ideation, Psychotic Ideation, Obsessive-Compulsiveness, and Sociopathy), whereas the remaining scales evaluated Self-Concept, Coping Attitudes, and Interpersonal relations (p.419-420). Overall, the test-retest reliability of the PEP was found to be acceptable (.67 to .87). The questionnaire was administered to all patients before therapy (baseline), two-week post-therapy, and two-month post-therapy (Ludwig & Levine, 1967).

A few days after the preparatory session, the treatment session took place. For all conditions, an "insight-interpretive" psychotherapeutic orientation was used. The patients were given a moderate to high dose of LSD (2-3 mcg/kg) orally without knowing what drug they would receive (Levine & Ludwig, 1965). Subsequently, they were told to relax as much as possible and hypnotic induction was administered. As a result of the time gap between the

administration and drug action of LSD, the effects of hypnosis (deep trance) and LSD were brought together in a very smooth manner. After this onset, the concentration of the patient declines and hypnotic induction becomes extremely difficult (Ludwig & Levine, 1967, p.134). The hypnotic relaxation enables the patient to better give in to the subsequent LSD experience and build as well as maintain a close relationship with the therapist. Eventually, the patient is instructed to share his or her feelings and the major problems previously identified are discussed (e.g., traumatic experiences). The demand characteristics of the hypnosis enable the therapist to structure, guide, and modify the psychedelic experience while discussing the problems of the patient. Finally, the therapist summarizes the important aspects and gives posthypnotic suggestions (e.g., make a greater effort in accepting responsibility). Next, the patient iss awakened from his or her trance and brought to another room where he or she spends the night. In case the patient desires to write about the experiences, pencil and paper are provided (p. 135).

The intergroup analysis showed that the hypnodelic therapy consistently produced greater improvement than any of the other four treatment conditions at both the two-week and two-month post-therapy intervals. The factor scores of the Psychiatric Evaluation Profile (PEP) for each of the five treatment conditions are displayed in Figure 1. This finding was most significant for the Self-Concept and Coping Attitudes scales two-weeks after the treatment (Ludwig & Levine, 1965). These two aspects are of relevance for addiction treatments. The "self-concept" is part of the ego-functions displayed by the DMN and impaired in patients with drug addiction.

Furthermore, addictions might develop as individuals are faced with stressful situations and fail to adapt emotional coping strategies (Rougement-Bücking & Grivel, 2014). In line with previous observations, the degree of suggestibility did not significantly correlate with the therapeutic results. However, a positive association was found between the intensity of an appropriate emotional abreaction (i.e., catharsis) and the reported benefit following therapy. Side effects and complications following the treatment techniques were less frequent than expected across conditions. If present, they included physical (e.g., insomnia, headaches, nausea, dizziness, and diarrhoea) as well as psychological (e.g., anxiety, agitation, and depression) symptoms. Nonetheless, they were described as manageable with routine hospital procedures such as sleeping medication for patients experiencing insomnia after the session (Ludwig & Levine, 1967).

The specific psychotherapeutic orientation that is used during the hypnodelic treatment technique may not be relevant as long as it is internally consistent and provides the patients with a framework that helps them understand their problems. Ludwig and Levine (1965 & 1967) used an insight-interpretive orientation with a psychoanalytic framework. However, there is no single theoretical orientation that fits the needs of every patient (Piper et al., 2002). The kind of psychotherapeutic orientation that is used also depends on the schooling and preference of the therapist. Nevertheless, the authors believe that the particular theoretical orientation is less important for therapeutic success than the general need of the patients to be provided with a framework that allows them to understand their

problems (Ludwig & Levine, 1967). Therefore, Ludwig and Levine (1965) believe that practically any theoretical orientation such as Jungian, Cognitivism, and Behaviourism would prove equally effective if the framework fits the current state of knowledge and is internally consistent.

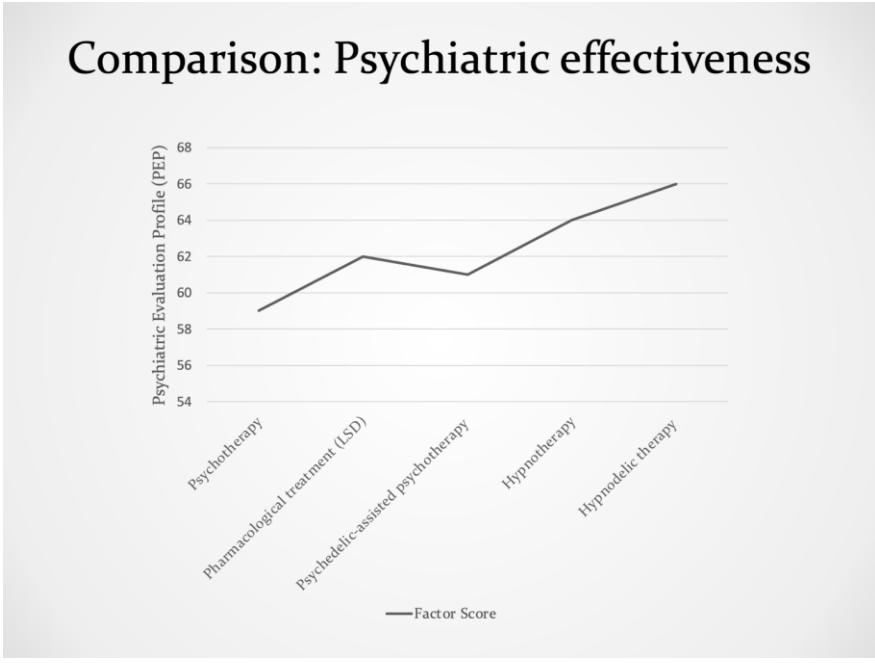

Figure 1. Comparison of the different treatment techniques employed by Levine and Ludwig (1965) and their effects on measurements of drug addiction. The Factor Score of the Psychiatric Evaluation Profile (PEP) is indicated on the y-axis for each of the following treatments: psychotherapy, pharmacological treatment (i.e., LSD), psychedelic-assisted psychotherapy (i.e., LSD and psychotherapy), hypnotherapy (i.e., hypnosis and psychotherapy), and hypnodelic therapy (i.e., hypnosis, LSD, and psychotherapy). Higher Factor Scores indicate less addiction (Ludwig & Levine, 1965).

Hypnodelic therapy shares some similarities with other "ultrabrief healing techniques" such as incubation and shamanistic

practices. These include, for instance, a sense of urge prior to therapy, emotional catharsis, suggestions, and explanations for the presented problems. These common denominators might represent the basis of any therapy to result in positive outcomes or "healing". Chiefly, what is believed to be a crucial prerequisite for therapeutic change in these healing practices is a disruption of normal consciousness and its underlying neural processes by altering the self-experience resulting in so-called "altered states of consciousness" (Ludwig & Levine, 1967; Millière, 2018).

Commonalities of hypnotic and psychedelic states

The psychological states induced by hypnotic suggestion demonstrate close resemblance to psychedelic states. The propensity to encounter mystical-type experiences correlates with hypnotic suggestibility (Spanos & Moretti, 1988). Although not all psychedelic drugs seem to enhance suggestibility, LSD does so to a similar extent as hypnotic induction (Carhart-Harris et al., 2015). The phenomenal response to psychedelics can not only be predicted by suggestibility but also by absorption. This individual tendency for experiencing intense attentional involvement occurs temporarily (Tellegen & Atkinson, 1974). Therefore, hypnosis and psychedelics have several phenomenological commonalities.

Despite their surprising similarities, psychedelics and hypnosis also demonstrate some differences. Psychedelics involve psychopharmacological processes and hypnosis occurs in an interpersonal context using suggestion techniques. Moreover, the

psychedelic experience is limited and time dependent on pharmacokinetic as well as pharmacodynamic processes (e.g., rate of metabolism and excretion of the drug). In contrast, hypnotic states can be maintained for as long as the patient and therapist intend to until termination is actively induced (Lemercier & Terhune, 2018).

There seems to be a converse association between the shared spontaneous phenomenological effects of the two phenomena (i.e., hypnodelic and psychedelic states) and global functional connectivity patterns. High connectivity seems to be associated with psychedelic induced ego-dissolution (Tagliazucchi et al., 2016). This ego-dissolution is correlated with loss of self-control, thought disorder, anxiety, and arousal (Studerus et al., 2011). In contrast, low connectivity seems to be associated with self-transcendent experiences induced by hypnosis (Cardeña et al., 2013). The magnitude of these transcendent experiences following hypnotic induction is typically small especially compared to the very intense ego-dissolution induced by psychedelics (Lemercier & Terhune, 2018). Moreover, an fMRI study found asymmetry of the frontal lobe connectivity during hypnosis (Lipari et al., 2012). These discrepancies in global functional connectivity and anomalous self-awareness following hypnotic induction and psychedelic administration may be explained by an inverted-U shape as shown in Figure 2. Therefore, the psychedelic enhancement of suggestibility may be due to an overlapping mechanism responsible for the individual differences in responsiveness to psychedelics and hypnotic suggestibility (Lemercier & Terhune, 2018).

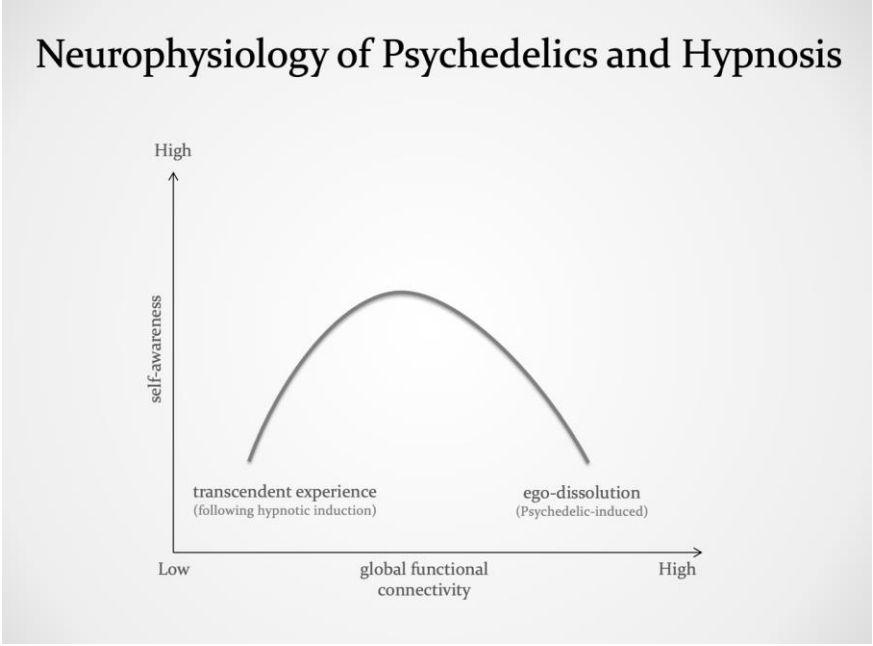

Figure 2. The graph displays a possible explanation for the discrepancies between spontaneous phenomenological effects of hypnosis and psychedelics (i.e., transcendent experiences and ego-dissolution) and their associated global functional connectivity patterns as proposed by C.E. Lemercier and D.B. Terhune (2018). Transcendent experiences seem to be associated with low global functional connectivity, whereas ego-dissolution seems to be associated with high global functional connectivity. Both phenomena represent aberrations of self-awareness.

Altered States of Consciousness during Hypnosis and acute LSD administration

Hypnosis and psychedelics might produce different altered states of consciousness (ASC). These alterations of consciousness may contribute to explaining the additive value of combining LSD and hypnosis in terms of neuropsychological processes. Another study by

the authors Levine and Ludwig (1965) investigated whether hypnodelic therapy results in more alterations of consciousness in patients with drug addiction compared to the other treatment conditions described previously. It seems important for the patient to keep the eyes closed in order to cut off the primary channel of perceptual feedback (i.e., vision) which in turn increases the alterations in consciousness (Ludwig & Levine,1967). To study the differences between these conditions, they used the Linton-Langs Questionnaire consisting of 73 items on seven scales on three points of time (pre-treatment, under hypnosis, and two-hours after the start of the session) to examine changes in the states of consciousness (Levine & Ludwig, 1965, p.124). The scale analysis showed that the hypnodelic therapy produced, by far, the greatest alteration in consciousness. Subjects in this condition reported a greater loss of control and body image change than subjects in the other four conditions. Furthermore, a different distortion of time sense, altered thinking, and somatic change were expressed in these subjects compared to three of the four remaining conditions. Surprisingly, the psychedelic condition, the psychopharmacological condition, and the hypnotherapy condition did not differ significantly from one another. However, these conditions can still be differentiated from the psychotherapy condition and the baseline measurements (PEP results before therapy; p.135). These findings support Gubel's claim that hypnosis and the subjective experiences of LSD are similar to each other. Altogether, the alterations of consciousness among these five conditions are visualized in Figure 3 and can be described in the following descending order: Hypnodelic therapy > (Psychedelic

therapy, Psychopharmacological treatment, Hypnotherapy) > (Psychotherapy, Baseline measurements). These findings might indicate that the greater alteration of consciousness enabled greater improvements.

Altered states of consciousness can be therapeutically effective. Field (1992) proposed five mechanisms by which ASC can increase therapeutic benefit. Stress reduction or the lowering of tension is achieved through sleep and other states of relaxation. The second mechanisms, release of bad objects, includes confessions but also the lesson that feared situations from the past can have a different outcome. Next, ASC can help to restore emotional experience in order to rebuild basic trust and foster self-acceptance. Furthermore, ASC can facilitate the working alliance between the therapist and the patient. Last but not least, ASC enhance creativity (Field, 1992). However, it is currently unknown whether a linear relationship between alterations of consciousness and therapeutic efficacy exists.

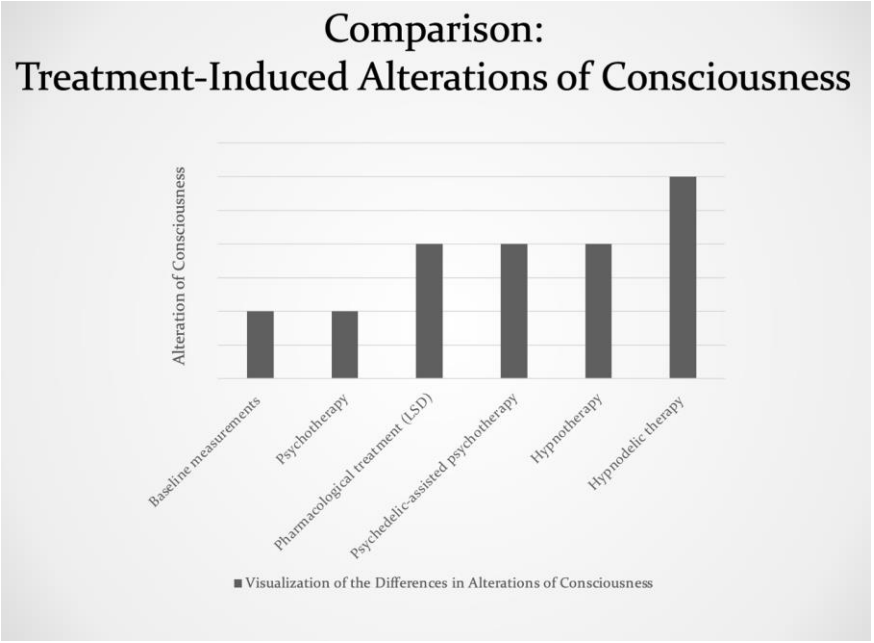

Figure 3. Visualization of the different treatment techniques employed by Levine and Ludwig (1965) with regards to their induced alterations of consciousness in patients with drug addiction. Baseline measurements and psychotherapy produced the least alterations and were not significantly distinguishable from each other. Psychedelic therapy, pharmacological treatment, and hypnotherapy showed similar alterations of consciousness which resulted in more altered states of consciousness than the other two. Finally, hypnodelic therapy significantly produced the most alterations of consciousness (Ludwig & Levine, 1965).

DISCUSSION

Psychedelics and hypnosis are both socially controversial and sensitive topics. Their combination (i.e., hypnodelic therapy) is probably even more controversial. This review intended to examine the potential efficacy of this treatment for addiction by first discussing hypnotherapy and psychedelic therapy on their own before moving on

to their combination. Hence, this line of reasoning should clarify whether hypnodelic therapy might have an additive value for psychotherapeutic outcomes. Despite its exploratory nature, this review offers some insight into the hidden potentials of psychedelics and hypnosis.

Hypnotherapy has proven to be an effective treatment for drug addictions. The American Medical Association (AMA) has accepted hypnosis as a medically valid tool. This treatment technique was specifically implemented as treatment for alcoholism over a century ago. Hypnosis can be applied to augment abstinence and prevent relapse by altering cognitive and behavioural processes (Pekala, 2016). According to the dynamic model of relapse by Witkiewitz and Marlatt (2004), relapse can be predicted by intrapersonal determinants and interpersonal determinants. The intrapersonal factors include cravings, coping skills, emotional states, motivation to change, self-efficacy, and outcome expectancy. The interpersonal factors include positive social support as well as negative peer pressure (Witkiewitz & Marlatt, 2004). Hypnotic suggestion can modify these factors to promote recovery, for instance, by increasing self-esteem or reducing and controlling negative Affects (e.g., anger, anxiety). Hypnosis and self-hypnosis also offer addiction patients the means to achieve a healthier or more productive altered state of consciousness. Overall, hypnotic suggestion can be an effective adjunct in the treatment of addiction and relapse prevention (Pekala, 2016).

Psychedelics have also demonstrated therapeutic potential and may have specific applications for patients with drug addiction. The Model of Possible Change Mechanisms in Hallucinogen-Assisted

Treatment of Addictions by Bogenschutz and Pommy (2012) suggests that there are four levels ultimately resulting in reduced substance use. The patient (set), the psychedelic substance, and the setting determine the treatment situation. Each psychedelic substance has acute effects which can be split in two dimensions. The acute physiological effects are primarily mediated by serotonin receptors and affect glutamate receptors. The acute psychological effects consist of the subjective experience such as a mystical experience. Persistent changes of psychedelics include improved mood, diminished anxiety, changes in beliefs and values as well as personality changes. Potential persistent functional or neuroplastic changes following psychedelic treatment have not been studied yet. Finally, an increase in motivation and self-efficacy with an additional decrease in craving are theorized to be the last mechanisms of change resulting in reduced substance use (Bogenschutz & Pommy, 2012). Psychedelics demonstrate low toxicity and non-addictiveness. Moreover, a single dose of psychedelics has significant, long-term beneficial effects (Burdick & Adinoff, 2013). Hence, psychedelics represent a safe and effective pharmacological intervention for patients with drug addiction.

Combining hypnosis with psychedelic-assisted psychotherapy may be more effective than each of these treatment techniques alone. Because of the observed phenomenological and neurophysiological similarities between psychedelic and hypnotic states, it was hypothesized that hypnosis could be used to modulate the LSD experience and, consequently, increase its psychotherapeutic efficacy. The findings suggest that, in general, hypnodelic therapy produces greater improvement in patients with drug addiction than any other

combination of these treatment techniques (i.e., hypnotherapy, psychedelic therapy, only LSD, or psychotherapy; Ludwig & Levine, 1967). It was also shown that it produces the strongest alteration of consciousness compared to the other four conditions (Levine & Ludwig, 1965). A greater alteration of consciousness can be beneficial for therapeutic outcomes by the means of stress reduction, release of bad objects, restorative emotional experience, facilitation of the working alliance between the therapist and the patient, as well as the enhancement of creativity (Field, 1992).

The observed phenomenological and neurophysiological similarities of hypnosis and psychedelics (Gubel, 1962; Lemercier & Terhune, 2018) could contribute to their harmonious interaction as a combined treatment technique. More specifically, comparing hypnotic and psychedelic states shows that both treatment techniques affect the activity of several brain areas including the prefrontal cortex (PFC) and cingulate cortex (CC). However, psychedelics do affect a larger set of brain regions with subsequent broader changes compared to hypnosis. Especially the frontal regions, medial temporal lobe, occipital cortex (OC), hippocampus, and amygdala are affected by psychedelics (Ly et al., 2018). Both hypnosis and psychedelics decrease the activity and increase the connectivity in parts of the DMN or with other networks (Cardeña, et al., 2013; McGeown et al., 2009; Pasquini et al., 2020). Finally, both hypnosis and LSD have been found to promote neuronal plasticity which is suggested to underlie the antidepressant and anxiolytic effects (Ly et al., 2018) beneficial for psychotherapeutic outcomes.

Hypnodelic therapy may be particularly effective as treatment for drug addictions. Not only have both hypnotherapy and psychedelic therapy demonstrated to be effective, but they also address different aspects of the multi-dimensional process leading to recovery. Hypnosis can be used to modify cognitive and behavioural processes such as cravings and self-efficacy to augment abstinence and prevent relapse (Pekala, 2016). Psychedelics have neurophysiological effects that improve mood and diminish anxiety (Bogenschutz & Pommy, 2012). Mystical experiences could give patients new insights and motivation to change through consciousness raising (Bogenschutz & Pommy, 2012). Some of the effects of hypnosis and psychedelics on the recovery process of addiction do overlap (e.g., self-efficacy, improved mood) while each of them addresses additional aspects that promote recovery. For instance, hypnosis can help with coping skills and psychedelics can induce personality changes (Bogenschutz & Pommy, 2012; Witkiewitz & Marlatt, 2004). Thus, psychedelics and hypnosis are potential complementary adjuncts to psychotherapy as treatment for addictions.

The current review is limited by the lack of information on the relatively latent treatment technique due to a drastic decline in scientific interest caused by the prohibition of LSD in 1970. Only one recent article tried to revive the scientific interest in hypnodelic therapy (Lemercier & Terhune, 2018). Additionally, most studies included in this review investigated certain types of addiction (e.g., narcotic, opiates) and reported small sample sizes which limits the generalisability of findings to other substance related addictions (e.g., nicotine). Additionally, Ludwig and Levine did not include a placebo

control group as it would have been unethical to deny a patient recommended for psychotherapy some form of treatment. Nowadays, this dilemma is mainly solved by including wait-list controls. Without a control group, it may be that the observed changes are at least partly due to the nonspecific effects of milieu and time instead of therapy per se (Ludwig & Levine, 1965) or represent a placebo response. The authors were not blinded to conditions. Moreover, a social desirability bias cannot be excluded due to self-deception. This might especially be the case for the measurements of alterations of consciousness because the questionnaires are not able to objectively measure the validity of a patient's response. However, only considering the subjective response reliably measures the quantity of several subjective effects (Ludwig & Levine, 1965).

Notably, the first hypnodelic studies used psychedelic therapy which is no longer popular. The original psychedelic therapy that originated in America and Canada involved high doses of psychedelic substances (e.g., 400-500 µg of LSD) which are only administered once. The American psychedelic therapy is intended to create and focus on the "overwhelming" mystical experience (e.g., patients were able to write about their experiences after the session). This approach shares many similarities with religious mystical experiences and represents a symptomatic cure. In contrast, the European "psycholytic" therapy uses lower doses of psychedelic substances (e.g., 30-200 µg of LSD) throughout several sessions in order to activate and deepen psychoanalytic processes. The psychedelic experiences are analytically discussed and then compared to reality. This helps the patient to adapt their experiences to everyday life and integrate them

meaningfully (Majic et al., 2015). Ultimately, psycholytic therapy aims to reconstruct the personality by loosening of infant-parent attachments and learning of healthy coping mechanisms (i.e., "maturing process"). Notably, the psycholytic approach is more similar to our currently implemented psychedelic-assisted psychotherapy models than the original American psychedelic therapy. Therefore, it is important to distinguish between those two approaches when reviewing psychedelic studies.

The simultaneous and combined use of psychedelics and hypnosis is not the only promising way these treatment techniques can be used to improve therapeutic outcomes. In order to prevent bad trips and increase the probability of desirable outcomes, naïve patents could be familiarized with the effects of psychedelics by the means of a hypnosis-based training in a safe environment. This would not only reduce the degree of anticipated anxiety but also augment the positive response expectancies of the psychedelic experience (Lemercier & Terhune, 2018). Furthermore, hypnosis could be used to re-experience the psychedelic states in the following days after the administration without the need of the drug itself (Hastings, 2006). This would provide additional opportunities for the patient to explore and utilize the positive aspects of the psychedelic experience potentially enhancing the psychotherapeutic outcomes especially in the long-term (Lemercier & Terhune, 2018).

Although this review summarised the literature critically, there are still many questions in need of further examination. For instance, Ludwig and Levine (1967) argue that therapists who are quite familiar with the physiological as well as the psychological effects of

LSD and hypnosis could apply the hypnodelic treatment technique best. Thus, a standardized program for training professionals of specific mental health and medical sectors is needed to advance psychedelic-assisted psychotherapy research (California Institute of Integral Studies). Since not every therapist is trained (well) to apply these techniques, the studies mainly examined psychotherapeutic efficacy (ideal conditions) instead of effectiveness (real-world settings). Future research should, therefore, study psychotherapeutic effectiveness of the hypnodelic treatment technique. Additionally, it is important to compare the efficacy with conventional therapies in order to determine how promising the results are de facto. Furthermore, it is not clear yet how persistent the observed changes in attitude are (long-term follow up studies) and how these relate to actual behavioural change.

More research is needed to better understand the relationship between psychedelic and hypnotic states. For instance, this review only focusses on LSD but other psychedelic drugs such as psilocybin ("magic mushrooms") or mescaline (peyote cactus) might have similar or dissimilar effects. Currently, it is not known what dosages are required to enhance suggestibility in patients and it may be possible to reduce the dose to a minimum without devaluing therapeutic outcomes (Lemercier & Terhune, 2018). Future research should also establish which patients or psychiatric conditions are most suitable for this treatment technique as the hypnodelic studies excluded patients who were overtly psychotic, had serious physical illness or more than minimal organic brain damage (Ludwig & Levine, 1967). Finally, more research is needed to bring about the long overdue policy changes and

make these treatments accessible to the patient populations (e.g., patients with drug addiction, depression, and anxiety) that could benefit from them.

CONCLUSION

Both psychedelic therapy and hypnotherapy have been proven to be effective treatments for addictions in the past. The combination of the two treatment techniques is likely to have an additive value partly due to their phenomenological and neurophysiological similarities such as the promotion of neuronal plasticity. Not only have both hypnotherapy and psychedelic therapy demonstrated therapeutic potential, but they also address different aspects of the multi-dimensional process ultimately leading to recovery. Hypnodelic therapy seems to be a promising treatment technique for patients with drug addiction. Hence, hypnodelic therapy deserves renewed scientific interest and has important implications for clinical practices. However, more research applying the modern standards of RCTs and statistical power for clinical trials is needed to determine its actual psychotherapeutic efficacy.

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This paper is the product of students from the Faculty of Psychology and Neuroscience, Maastricht University and is meant for student educational purposes only.

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Neurobiological Correlates of Decision-Making in Framing Conditions

Original research

Human decision-making is a complex process and often influenced by emotionally relevant information. To date, the associated neurobiological correlates are not well understood. Previously, De Martino et al. (2006) assessed the effect of framing on decision-making. The framing effect, which is part of Prospect theory, refers to a cognitive bias leading to differential decision-making based on the context and the connotation that information is presented in. The current study aimed at replicating De Martino et al.'s findings and thus supporting the hypothesis that decision biases occur when framing information and that increased amygdala activation underlies such emotional responses. Participants performed a computerised task in which they were first presented with an initial starting amount of money

and then underwent different trials consisting either of deciding between gambling and keeping or gambling and losing a certain amount of money. The task was performed both outside and inside a 3T fMRI scanner by separate groups. Behavioural results indicated a tendency to act in accordance with the frame. fMRI analysis revealed no increase in amygdala activation when complying to the bias. When making frame-incongruent decisions, increased anterior cingulate cortex (ACC) activation was established. Increases in ACC activation can be related to acting in a more rational instead of emotional manner. Furthermore, activity in the cerebellum was increased when making a choice, indicating the involvement of this brain area in decision-making under uncertainty.

Keywords: decision-making, framing effect, amygdala, rationality, gambling

INTRODUCTION

The underlying mechanisms of human decision-making have been of great interest for several decades. Multiple theories, such as Game theory and Prospect theory, have been postulated attempting to explain and predict decision-making. The proposition of Game theory by Morgenstern and von Neumann describes a decision maker´s behaviour in terms of a mathematical utility function and assumes rational decision-making (Osborne & Rubinstein, 1994; Von Neumann & Morgenstern, 1944). This theory is applied in instances where strategic thinking is used, for example in the field of social sciences, such as business, economics, and politics (e.g. war strategies) (Riechert & Hammerstein, 1983).

Despite the theory's applicability in some of the fields mentioned above, Kahneman and Tversky encountered several examples in which the theory's axioms including descriptive invariance and rationality were violated. This led to the development of Prospect theory, a non-utility theory which explains human decision-making by not assuming rationality only. One central concept of the theory is the framing effect which refers to the phenomenon that the context an option is presented in, alters choice behaviour (Kahneman & Tversky, 1979). For example, a choice may depend on whether something is to be lost or gained, as these two scenarios are evaluated differentially (defined as loss aversion in Prospect theory) (Kahneman & Tversky, 1979; Schindler & Pfattheicher, 2017).

The cognitive framing bias has been observed in several societal contexts (Kahneman & Tversky, 1984; Piñon & Gambara, 2005; Tversky & Kahneman, 1981). For instance, in the health-domain it has been demonstrated that decisions by doctors and patients are influenced by the frame that information is presented in. When a person was presented with a positive (40 percent chance of surviving) instead of a negative frame (60 percent chance of dying) they were more likely to agree to surgery in the positive frame (Marteau, 1989). In the field of consumer behaviour, biased decision-making due to framing is often observed. For example, evaluations of ground beef were better when the product was presented as "80% lean meat" compared with "20% fat meat" (Levin & Gaeth, 1988). Abovementioned examples emphasise that humans rarely make decisions strategically and instead often misinterpret information due to a cognitive framing bias. These findings illustrate that Prospect theory is more suitable than Game theory in explaining daily decision-making.

It is postulated that the aforementioned bias occurs due to a trade-off between cognitive effort and affect (Gonzalez et al., 2005). In line with this is Dual Process theory. The main assumption is that rapid, autonomous processes are properties of an emotional system (system 1) and yield default responses unless a second rational and deliberate system (system 2) intervenes. System 1 is expected to lead to biases and heuristics in decision-making (Evans & Stanovich, 2013). System 2 in turn counteracts biases and becomes active when engaging in rule-based decision-making. System 1 has been found to correlate with increased amygdala activation. System 2 has been found

to correlate with prefrontal cortex (PFC) activation, which also correlates with higher order reasoning processes in different situations (Murch & Krawczyk, 2014; Roiser et al., 2009). Despite indications that amygdala and PFC activation may be related to the framing effect, this link has not been assessed yet.

Several lines of research on amygdala and PFC activation indicate a potential involvement of the two brain areas in the framing effect due to their link with system 1 and system 2. For example, amygdala activity is often associated with emotional and fear processing, and reward processing (Adolphs et al., 1994; Adolphs et al., 1995; Davis, 1992; Hampton et al., 2007; LeDoux, 2003; Whalen et al., 1998). Moreover, the amygdala mediates stimulus-value associations which play a role in decision-making in framing conditions (Baxter & Murray, 2002). Distinct neural populations that associate a positive and negative value with the presented stimuli have been observed in the amygdala (Paton et al., 2006).

The PFC has been linked to rational decision-making and activity in the area has been shown to correlate with an individual's susceptibility to framing (Deppe et al., 2005). Additionally, the two brain areas seem to be connected anatomically and functionally. It has been demonstrated that amygdala input to the ventromedial PFC modulates reward-related signals and signals associated with behavioural choice in the prefrontal region (Hampton et al., 2007). Based on abovementioned findings, the amygdala and the PFC are hypothesised to show increased activation when making frame-congruent (system 1) and frame-incongruent choices (system 2) respectively.

To test these two hypotheses, a behavioural gambling task, consisting of either a loss or a gain frame (losing a certain amount of money; gaining a certain amount of money), was performed while recording the haemodynamic response using functional magnetic resonance imaging (fMRI). Beforehand, another group of participants performed the behavioural task to establish whether a framing effect would be observed using the paradigm. It was hypothesised that decision-making will be predominantly done in a frame-congruent manner (choosing the gambling option in the loss frame and the sure option in the gain frame) instead of being frame-incongruent (choosing the sure option in the loss frame and the gamble option in the gain frame) due to loss aversion (Kahneman & Tversky, 1979; Schindler & Pfattheicher, 2017). It was expected that people were more willing to accept a riskier option when confronted with a negatively stated alternative (loss frame) as compared to a positively stated one (gain frame). By recording responses in the behavioural task and haemodynamic changes in the fMRI scanner, the current study aimed to reproduce the functional role of the amygdala in the process of decision-making in framing conditions, suggested by De Martino et al. (2006).

METHODS

Two studies were conducted and are described in separate sections below. A behavioural study was conducted in order to assess the effect of framing on decision making with a sufficiently large sample size.

Another, small-scale fMRI study attempted to identify brain regions mediating this framing effect, aiming to replicate De Martino et al. (2006)'s findings.

Behavioural Study

Participants

Thirty healthy university students were recruited from the second-year cohort of the psychology bachelor at Maastricht University. The mean age was 21.4 years (± 1.7), and exclusion criteria included colour-blindness and participation in the fMRI study. Participants received compensation in the form of course credits. The study was approved by the Ethics Review Committee Psychology and Neuroscience (ERCPN). The reference number, both for this part of the study and the fMRI study described later, was RP2027_2019_33.

Materials

A computerised behaviour task was used, and responses were made via a keyboard. As the study aimed to replicate De Martino et al. (2006)'s procedure, an adjusted version of that code was used, which the researchers had published on GitHub (Folke, 2015).

Procedure and Design

The experimental paradigm consisted of a financial decision-making task in which the effect of the independent variable "Frame" on the dependent variable "Choice" was assessed. A within-subjects design

was used in which all participants underwent all conditions (positive and negative framing), which each consisted of 95 trials. Due to the nature of the framing effect, participants were given incomplete information during the briefing, i.e. they were merely told that decision-making was being assessed. Furthermore, to ensure that there was an incentive to achieve a high score despite the lack of a real monetary reward, participants were promised different non-monetary prizes depending on their score. Following the briefing, each participant underwent a practice round before the main task, and a debriefing afterwards. The task itself consisted of 190 trials, distributed over three blocks separated by short breaks. Additionally, 20 so-called "catch trials", in which one choice was objectively preferable, were included per condition in order to assess whether participants understood the task.

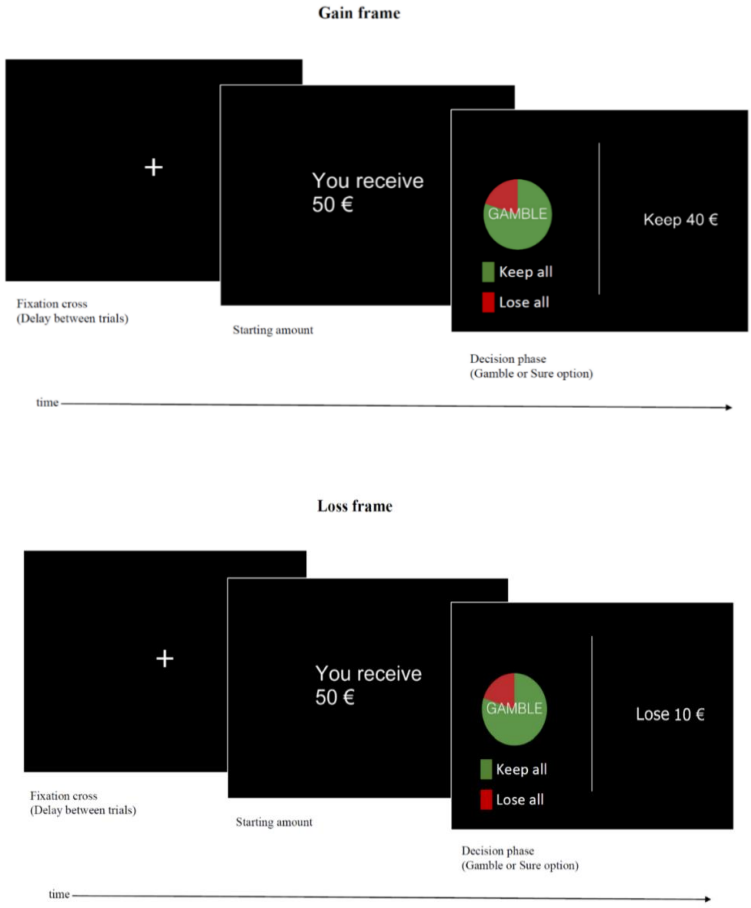

Figure 1: Stimulus Example. Overview of the course of a single trial in each experimental condition.

Each individual trial begun with a display of the initial or starting amount of money, worded as "You receive X€". This amount took the form of four different values (25€, 50€, 75€, 100€), balanced across all conditions. This was displayed for 1s followed by a delay of 0.5s before the next display, constituting the decision phase of 2.5s (Figure 1). Subjects had two choice options: "Gamble" or "Sure", that were

displayed on either side of the screen. The Sure option stated how much of the starting amount of money can be kept for sure, and also incorporated the framing manipulation. This frame consisted of the message "Keep X€" ("Gain" frame) or "Lose X€" ("Loss" Frame). The Gamble option displayed a pie chart showing the probabilities to either "Keep all" (coloured green) or "Lose all" (coloured red), which was the case for both frames. The probability of winning the full starting amount took one of four different values (20%, 40%, 60%, 80%), which were balanced across all conditions.

The expected outcome of both choice alternatives (i.e. Gamble or Sure) was always equivalent, that is the proportion of money relative to the starting amount one would receive in the Sure choice option was equal to the probability of winning the full starting amount in the Gamble option. The only exception to this were the aforementioned catch trials, in which the winning probability in the Gamble option was either 95% or 5%, making one of the choice alternatives obviously preferable. After indicating their choice via pressing the arrow buttons on a keyboard, a brief delay or fixation cross period (1.5s) followed before the next trial.

As compared to the original study by De Martino et al. (2006), less catch trials were used in order to increase the power of the analysis. Furthermore, the original 4s maximum decision time was decreased, to avoid possibly giving the participants, all psychology students, too much time to become aware of the framing manipulation. The framing effect, in line with dual-process theory, is hypothesised to affect the intuitive system, which is faster and hence more prominent under time pressure (Guo et al., 2015; Guo et al., 2017).

In order to investigate the framing effect, this system should therefore be employed in the respective decision-making task. By decreasing the decision time, participants were forced to decide intuitively.

Data Processing and Analysis

In order to assess the main effect of frame, choice frequencies were transformed into percentages. For instance, the number of times a participant chose the gamble option in the loss frame condition was expressed as a percentage of all responses within the loss frame. For the statistical analysis a paired samples t-test was used, comparing the percentage of gamble choices in each frame. Furthermore, a one-sample t-test was used to test for both frames the null hypothesis that participants were risk-neutral (i.e. chose both choice options 50% of the time).

In addition to the main effect, possible effects of the four different values of "Starting Amount", as well as "Winning Probability" were examined. For this, percentages of gamble choices in the total trials of the four starting amounts (i.e. 25€, 50€, 75€, 100€) or winning probabilities (i.e. 20%, 40%, 60% 80%) were calculated, again for each frame separately. For instance, the percentage of a participant's gamble choices in all trials of the gain frame in which the starting amount was 25€ was calculated. The effects of starting amount and winning probability were then each separately assessed using two-way repeated measures analyses of variance, in order to check both for possible main effects of starting amount and winning probability as well as interaction effects with the framing condition.

For the purpose of comparing the extent to which participants were susceptible to the framing effect, also across the two studies, a rationality index was computed for each subject (Table 2). This was modelled after De Martino et al. (2006)'s operationalisation of rationality, which was defined by choosing the gamble option as often in the gain frame as in the loss frame. Hence the absolute value of the difference between proportions of gamble choices that occurred in the loss frame and in the gain frame was taken, and transformed so that a value of 1 indicates a complete indifference to the framing effect (i.e. equal distribution of gamble choices in both frames) while a value of 0 implies being heavily influenced by the effect of frame, so that one chooses to gamble only in either one of the frames.

fMRI Study

Participants

Eight healthy university students were recruited in line with scan time restrictions which did not allow more participants to be tested. The sample consisted of both males and females, right- and left-handed, with a mean age of 21.9 years (± 2.0). Exclusion criteria for participation included colour-blindness as well as having participated in the behavioural study. Additionally, general exclusion criteria for participation in fMRI studies applied, which were assessed using a standard safety screening form. Participants were compensated with course credits. The study was approved by the Ethics Review Committee Psychology and Neuroscience (ERCPN), and the MRI

procedure was also authorised by a Project Proposal Meeting committee.

Materials

The same computerised behaviour task and stimuli as described in the behavioural study section were used. Brain activity was measured with a Siemens Prisma 3 Tesla magnetic resonance scanner. Participants gave their responses via MRI-compatible keypads, one for each hand.

General Procedure and Design

The same experimental paradigm as in the behavioural study was used with some alterations. Most importantly the delay between trials, during which participants had to focus on a fixation cross, was longer (5s) in order to capture the haemodynamic response. Furthermore, the catch trials were removed to take full advantage of the limited scan time. In total, participants in this study underwent 192 trials, 32 per framing condition per run. The practice round was completed outside the scanner prior to measuring, and the briefing included information about fMRI. During a one-hour scan time, anatomical measurements were taken, followed by 3 functional runs separated by breaks. Furthermore, the BOLD signal constitutes the dependent variable in the fMRI study, while the behavioural decision was used as a classification factor in addition to the experimental factor Frame.

Image Acquisition, Processing, and Analysis

Gradient-echo T2*-weighted functional data with a voxel size of 2mm3 and T1-weighted structural data with a voxel size of 1mm3 were acquired with a 3 Tesla MRI scanner. A multiband pulse sequence was employed, with a repetition time (TR) of 650ms. Slices of 2mm thickness were scanned in an interleaved fashion. The first 2 volumes were discarded during scanning in order to compensate for T1 saturation effect. This resulted in a total of 1020 volumes per run. The echo time (TE) was 28ms.

The data was analysed using BrainVoyager software (Goebel et al., 2006). Preceding the statistical analysis, the data was pre-processed. In an initial step, distortion correction was applied to the data using COPE (correction based on opposite phase encoding), a BrainVoyager Plugin (Andersson & Skare, 2002). Slice scan time correction and 3D motion correction was applied to the functional magnetic resonance data,. The resulting motion parameter time courses were later also integrated in the statistical analysis as a confound predictor to remove residual motion artefacts. Further, 3D Gaussian spatial smoothing was applied with a full width at half maximum (FWHM) value of 8mm. Lastly, a temporal band-pass filter using a fast Fourier transformation algorithm (FFT) with a cut-off value of 3.0 cycles was implemented. For the anatomical volumetric magnetic resonance (VMR) data, intensity inhomogeneities were corrected, and the images were transformed into Talairach space. Finally, FMR and VMR data were aligned using boundary-based registration.

Due to the small sample size, a fixed effects statistical analysis was used. It should be noted that while this boosts power enormously, results only apply to the sample studied. A general linear model was employed, using various contrasts between conditions to assess effects of interest. For example, the contrast between activity in frame-incongruent and frame-congruent choices was examined. Correction for multiple comparisons was made using a false discovery rate (FDR) cluster threshold. Time courses were normalised with a baseline z standardisation. Lastly, a correction for serial correlations was applied. The design matrix included all expected variance, that is all four frame-choice combinations or conditions, as well as several predictors of no interest, e.g. a no response condition for trials in which participants failed to respond quickly enough, and motion parameters obtained during motion correction.

Several contrasts were then assessed within the GLM model. Firstly, the main effect of the frame was examined, that is gain and loss conditions were compared. Furthermore, De Martino et al. 's (2006) interaction contrast as well as reverse interaction contrast was realised via a conjunction of the two contrasts GainSure versus GainSure and LossGamble versus LossSure. The reverse interaction contrast, for example, thus took the following form: [(GainGamble + LossSure) – (GainSure + LossGamble)]. Additionally, the latter effect was also examined further by checking each of the two contrasts individually. Behavioural effects were analysed as described for the behavioural study, using SPSS (IBM Corp, 2017).

RESULTS

Behavioural Outcomes

In line with our predictions, the frame effect was shown to be robust. Confirming the results of De Martino et al. (2006), the manipulation had a significant influence on the gambling behaviour (Fig.1). On average, subjects chose the gamble option 15,5% more often within the loss frame compared to the gain frame (56,9% > 41,4%), $t(29)=6.924, p<.001$. Additionally, subjects were biased towards risk aversion in the gain frame and risk neutrality in the loss frame, but a trend towards risk seeking could be observed in the data. These results are in accordance with Prospect theory, which, in contrast to Expected Utility theory proposes that the presence of rationality is not absolute in human decision-making (Kahneman & Tversky, 1979; Von Neumann & Morgenstern, 1944).

Furthermore, it was analysed whether the amount of money that was at stake would interact with the frame manipulation. Even though the starting amount had a significant effect on the decision when it was initially presented within the gain frame, the frame effect alone showed to be robust across different starting amounts. This also applies to the varying winning probabilities. Although the winning probability influenced the gambling behaviour (Fig. S2), the effect of the frame was still expressed.

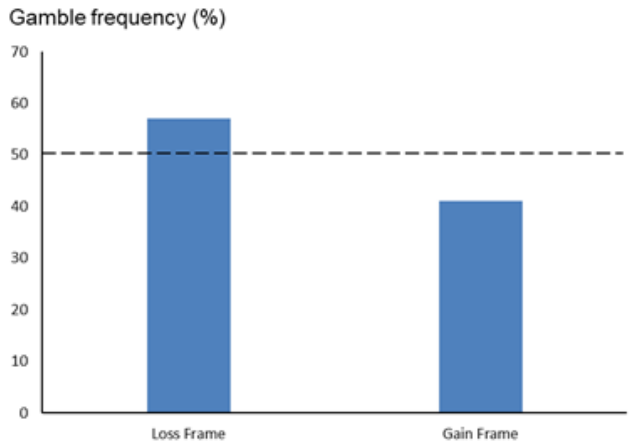

Figure 2: Gamble Frequency. Frequency of gambles within the loss frame and the gain frame, across conditions. Subjects chose the gamble option significantly more often when they were initially presented with the loss frame. The dashed line expresses risk-neutrality, which is marked by taking the gamble option in 50 percent of trials (De Martino, Kumaran, Seymour & Dolan, 2006). Additionally, subjects showed to be risk averse in the gain frame $t(29)=2.292$, $p = .029$, and risk neutral in the loss frame $t(29) = 1.6$, $p = .12$ (i.e. hypothesis that risk seeking is pronounced within the loss frame is not supported).

Catch trials and awareness of manipulation

Subjects performed highly accurate on catch trials (Fig. 3), providing evidence for sustained attention and involvement with the task. Moreover, only two subjects reported that they noticed the framing manipulation. Results can therefore be interpreted meaningfully.

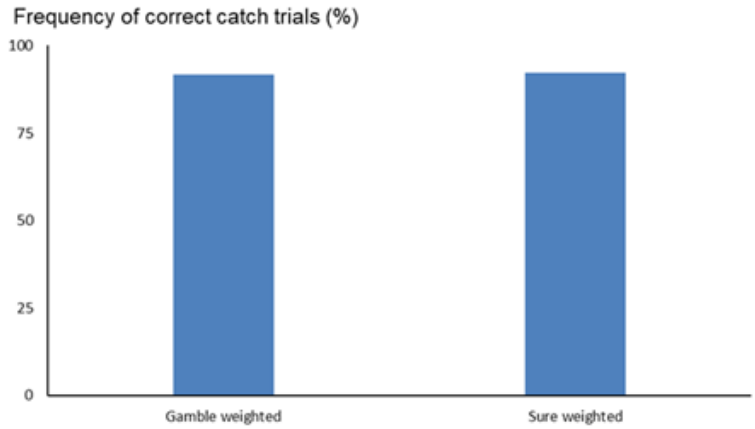

Figure 3: Frequency of Gambles in Catch Trials as Function of Choice Utility. In the 'gamble weighted' condition, the probability of winning was set to 95%. Irrespectively of the frame, the subjects were expected to choose the gamble option to make the optimal choice. In contrast, in the 'sure weighted' condition the winning probability was 5%. Here, the best choice was to choose the sure option. The number of correct trials (bars) displays the high accuracy of the subjects in choosing the better option (gamble weighted = 91,69 %, sure weighted = 92,22 %).

Analysis of fMRI Data

Amygdala activity has not been found to correlate statistically significant with framing. Within the key experimental contrast [(GainSure + LossGamble) – (GainGamble + LossSure), the amygdala was not significantly more active when subjects made decisions that were in accordance with the frame effect (GainSure and LossGamble).

The reverse interaction contrast was also of interest [GainGamble + LossSure) + (GainSure + LossGamble)]. This revealed significantly more activation in the anterior cingulate cortex (ACC) when subjects were not affected by the frame effect (GainGamble and LossSure; Fig. 3). Furthermore, it was examined whether this effect

could also be observed for each frame independently [(GainGamble) – (GainSure) and (LossSure) – LossGamble)] and it showed to be robust. The activation of the ACC was significantly greater when subjects chose the gamble option in the gain frame, (3,10,42),t=4.94,p<.00001, and the sure option in the loss frame, (-1,26,31),t=4.42,p<.0001.

In an additional analysis, the frames were contrasted with each other [(GainSure + GainGamble) + (LossGamble + LossSure)]. Interestingly, the ventromedial prefrontal cortex showed to be significantly more active when subjects were presented with the gain frame than with the loss frame, right hemisphere (3,56,6),t= 4.22,p<.001; left hemisphere (-1,53,5),t=3.71,p<.001].

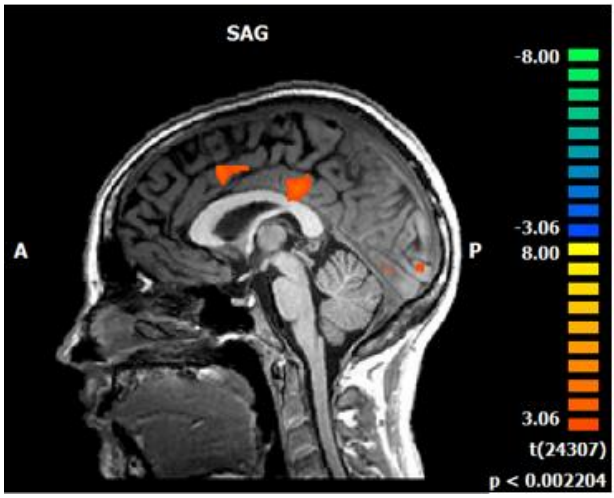

Figure 4: fMRI Results of the Decision Task. The reverse interaction contrast [(GainGamble + LossSure) - (GainSure + LossGamble)] reflected the following activity of the Anterior Cingulate Cortex, Talairach space coordinates (x, y, z]: left hemisphere -3, 8, 42 (t-value = 4.14); right hemisphere 2, 14, 41 (t = 3.82). The effect was significant at p < .0001. For display purposes it is shown at p < .002204.

Table 1: Brain Areas Significantly More Active During the Reverse Interaction Contrast [(GainGamble + LossSure) - (GainSure + LossGamble)]

Region	Laterality	x	y	z	t-value
Anterior Cingulate Cortex	L	-3	8	42	4.14
	R	2	14	41	3.82
Posterior Cingulate Cortex	L	-3	-25	30	4.10
Cuneus	L	-14	-72	12	4.23
Lingual Gyrus	R	12	-72	-5	4.18
Cerebellum	R	18	-71	-24	3.68

Table 2 Rationality Indices of fMRI Participants

Subject	Rationality Index
1	0,767676768
2	0,8169014084507042
3	0,6542056074766356
4	0,9268292682926829
5	0,9726027397260274
6	0,816901408
7	0,8888888888888889
8	0,9375
Mean	0,8477
Std. Deviation	0,10513

DISCUSSION

To investigate the hypothesised framing effect, we conducted a separate behavioural study before implementing the same

experimental paradigm in the fMRI scanner. The aim of the behavioural part was to investigate whether people are more willing to accept a riskier option when confronted with a negatively stated alternative (loss frame) as compared to a positively stated one (gain frame). The results of the behavioural experiment match the findings of De Martino et al. (2006) as a significant main effect for the framing manipulation was found. Participants chose the frame-congruent option (choosing the gambling option in the loss frame and the sure option in the gain frame) significantly more often than the frame incongruent one (choosing the sure option in the loss frame and the gamble option in the gain frame). This is in accordance with a study by Gonzalez et al. (2005), who found similar results. People proved to be more risk-seeking (i.e., choosing the gamble option more often) when confronted with negatively framed options (i.e., the loss frame) and more risk-averse when confronted with positively framed options (i.e., the gain frame), following the predictions made by Prospect theory (Kahneman & Tversky, 1979). Even though the obtained data reveals interaction effects in terms of winning probability (i.e., 20%, 40%, 60% 80%) and starting amount (i.e., 25€, 50€, 75€, 100€), the framing effect still proved to be existent.

Importantly, significant activation in the ACC was found during decisions that ran counter to the assumed framing effect. This corroborates findings of De Martino et al. (2006) who found the ACC to be activated in this context as well. A possible explanation for this activity comes from Rushworth et al. (2004) who state that one role of this brain area is to relate actions to their consequences. It is suggested that the ACC processes information about the expected consequence

of an action and whether this outcome is worth it to act upon. Since the activity was significantly more pronounced in the frame-incongruent conditions, this could reflect a tendency of the participants to not act upon the frame effect but to behave more rationally. Further, acting congruent to the framing effect or not could be related to the orbitofrontal cortex (OFC) and the ACC (Talmi et al., 2010). Stalnaker et al. (2007) propose that the OFC can be associated with cognitive flexibility which is needed in order to overcome risk-averse associations encoded in the amygdala. Therefore, future research should examine the role of the OFC and the ACC in decision-making under the influence of the framing effect.

Unexpectedly, our results revealed cerebellum activation could be seen when making "Sure vs. Gambling" decisions. Blackwood et al. (2004) showed that the cerebellum mediates probabilistic decisions made under uncertainty, which gambling behaviour can be linked to. This uncertainty may be induced by presenting a pie chart and prodding the participant to make an intuitive probabilistic decision on its basis (i.e., uncertainty regarding the outcome and probabilistic decision because of the pie chart). This supports the emerging view that the cerebellum is involved in more complex thought-processes (Schmahmann & Caplan, 2006).

Counter to our hypothesis and the findings of De Martino et al. (2006), no increased amygdala activation was found during frame-congruent behaviour. This is surprising given that other studies found a significant contrast between the conditions (Hampton et al., 2007; Murray, 2007; Roiser et al., 2009). Several reasons for this finding are suggested: first, due to restricted scanning hours, we were only able to

test eight participants. Because of that, the signal in the region of interest was not enough to acquire an acceptable signal-to-noise ratio (SNR), potentially explaining our null finding in terms of amygdala activation. Future experiments should try to recruit more participants to circumvent this risk. Additionally, slow event-related fMRI experiment designs such as the one used in the present study are prone to have a lower SNR in general, resulting in a loss of statistical power (Murphy et al., 2007). It is advisable that future studies expand the time spent in the scanner to allow for more time between the trials, which in turn would increase the statistical power, so that the haemodynamic response can set back to baseline.

Furthermore, the participants in the fMRI experiment were not susceptible to the framing and acted in a rational manner. The rationality indices of all eight participants were located in the upper half of the scale, therefore the sample might not have been heterogeneous enough in to detect differences in amygdala activity. Moreover, as a multiband sequence with a relatively fast TR was used (650 ms) our data is more sensitive to movement and artefacts (Boubela et al., 2014) We can therefore not recommend this sequence as it created most of the distortions in the medial part of the brain, which was our main area of interest. This might have had consequences for our data as a possible activation in the amygdala might be concealed by these distortions. Lastly, findings of amygdala activation have been found to be susceptible to confounders such as interplays between the scanner sequence settings and the specific properties of the tissue surrounding the region of interest (Boubela et al., 2015; Murphy et al., 2007).

In addition to the potential effects of our small sample on SNR, Turner et al. (2018) pointed out that moderate sample sizes might impede the adding up to the ongoing discussion about a possible reproducibility crisis (Aarts et al., 2015). To counteract the small sample size, we conducted an additional behavioural study using the same experimental paradigm and bigger sample size, which turned out to be significant. We therefore assume that the found framing effect in the fMRI analysis can be generalised. Additionally, subjects reported that the decision task got monotone after some time, probably due to its relative simplicity. Due to scanning constraints, catch trials to retain attention and counteract fatigue effects were not included in the fMRI experiment. It is advisable that future research incorporates a controlling factor to prevent possible confounding, for example computer game-like elements.

Even though our study does not provide clear support for the dual process theory, other studies found such evidence. A study conducted by Cassotti et al. (2012) found that the framing effect can be eliminated if the subject is shown a picture describing a positive emotional context. Strikingly, this study used the same experimental paradigm as De Martino et al. (2006), suggesting that this effect would probably also be existent in our experiment. In line with this finding is a study by Thomas and Millar (2011) who showed that when subjects are provided with additional information during the decision-making process they are less susceptible to the framing effect. This, on one hand, might be considered support for the dual process theory as it shows that a more deliberate system can overrule a predominantly emotional system, given that analytical behaviour is encouraged. On

the other hand, there might only be one system which is differentially modulated by the amygdala depending on the context.

An unexpected result was found by Talmi et al. (2010) who conducted a framing study with patients suffering from Urbach-White disease (UW) which is associated with bilateral amygdala degeneration. It was shown that UW patients were influenced by the loss condition to the same extent as the healthy control group. However, UW patients chose the riskier option more frequently in the gain condition as compared with the control group. Therefore, the researchers suggest that amygdala activity is more likely to be associated with conditioned risk-aversion rather than with the framing effect itself. Alternatively, it is possible that the amygdala is not solely responsible for the framing effect but rather that it modulates the system of cognitive processes which together lead to this bias in decision-making (Talmi et al., 2010).

Even though our study focused on decision-making in monetary settings, it can be applied to other contexts as well. Next to general media and commercial advertisements, framing has been of particular political interest in the past. Politicians are using framing in order to pursue their political goals and to convince potential voters. For example, former US president Donald Trump made use of framing in his election campaign by calling publications of the media "fake news", therefore discrediting them to attract voters (Vlatković, 2018).

Our study provides an extended framework for future research, as it shows that the brain processes underlying decision-making are still not fully understood. Nevertheless, we provide further evidence for the framing effect in terms of behavioural results. As a

dual process approach was neither accepted nor refuted, it is concluded that further research is needed in order to find out to what extent certain brain areas contribute to decision-making. Especially, research should try to focus on the question whether the neural underpinnings of decisions are rather subject to a dual system where the amygdala is active depending on the context or rather one system where the amygdala is always active but gets more active depending on the situation.

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