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Rewiring the impulsive brain

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Publication date:
2019

Document Version
Publisher's PDF, also known as Version of record

Link to publication in Tilburg University Research Portal

Citation for published version (APA):
Fielenbach, S. (2019). *Rewiring the impulsive brain: Neurofeedback treatment in forensic psychiatric patients with substance use disorder*. Netzodruk.

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Rewiring the impulsive brain: Neurofeedback treatment in forensic psychiatric patients with substance use disorder

Rewiring the impulsive brain:
Neurofeedbackbehandeling bij forensisch psychiatrische patiënten
met middelenafhankelijkheid

Sandra Fielenbach

Rewiring the impulsive brain

Neurofeedback treatment in forensic psychiatric patients with substance use disorder

Proefschrift ter verkrijging van de graad van doctor

aan Tilburg University

op gezag van de rector magnificus, prof.dr. E.H.L. Aarts,

in het openbaar te verdedigen ten overstaan van een

door het college voor promoties aangewezen commissie

in de aula van de Universiteit op vrijdag 1 maart 2019 om 10.00 uur

door

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geboren te Troisdorf, Duitsland

Promotor
Prof. Dr. S. Bogaerts

Copromotores
Dr. F.C.L. Donkers
Dr. M. Spreen

ISBN
978-90-829867-0-9

Cover & lay-out design
www.proefschriftopmaak.nl, Groningen

Print
Netzodruk Groningen

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Chapter 1

Introduction

In the Dutch legal system, individuals who have committed a violent crime and suffer from a mental disorder are sometimes held only partially responsible for the crimes they have committed. In some cases, the person is not held fully accountable for the committed crime because he/she was unable to grasp the full consequences of his/her actions due to the presence of at least one severe mental disorder. In this case, the individual who has committed the crime can be judged (partially) insane. The Dutch legal system knows five categories in which an individual can be considered insane, indicating the level of accountable responsibility for committing the crime. These categories range from 1) Fully responsible/ Not insane at all, whereby a mental disorder did not influence a person' s judgement at all to 5) Fully irresponsible/Insane for the crime due to the overruling effects of the mental disorder on a person's judgement. In cases of (at least partial) insanity, the judge can order the person to be treated on the order of the state. This system is called the Dutch Entrustment Act, or 'terbeschikkingstelling' (TBS) (van Marle, 2002). With a few exceptions, TBS can only be given for crimes with a minimal sentence of at least four years, indicating that the crime was characterized by a particular severity of violence, such as murder, manslaughter, arson or sexual offending. In cases where TBS is given, the judge considers the risk for criminal reoffending particularly high if the offender is not treated properly for his/her mental illness. The offender can then be submitted to an inpatient forensic psychiatric facility, and is, from this point forward, called a forensic psychiatric patient rather than an offender. The primary aim of the TBS sentence is to protect society and offer treatment that reduces the chance for criminal recidivism (van Marle, 2002).

In the Dutch general population, about 4 out of 10 people between the age of 18 and 64 have suffered or will suffer from a mental disorder at some point in their lives. The most common mental disorders in the Netherlands include mood disorders like depression or bipolar disorder, anxiety disorders, and substance use disorders (SUD's) (Trimbos, 2010). In prison populations, the prevalence of mental disorder is higher than in the general population. 50 to 80% of male prisoners are diagnosed with a personality disorder (e.g., Edens, Kelley, Lilienfeld, Skeem, & Douglas, 2015; Fazel & Danesh, 2002), with antisocial personality disorder being the most common. Personality disorders describe "an enduring pattern of inner experience and behavior that deviates markedly from the expectation of the individual's culture", with inflexible and pervasive patterns across a broad range of personal and social situations, which leads to significant distress or impairments in social, occupational or other important areas of functioning (definition of personality disorders DSM-5, American Psychiatric Association, 2013, p. 849). Often times, personality disorders are present in combination with other mental disorders. In 2011, a profiling study into the descriptive characteristics of forensic psychiatric patients in the Netherlands showed that these patients usually present with an average of 3.5 diagnoses per patient (Van Nieuwenhuizen et al., 2011). Most common disorders are SUD, schizophrenia, attention-deficit/hyperactivity disorder (ADHD), impulse control disorders, and cluster B personality disorders, such as antisocial, borderline or narcissistic personality disorder (Van Nieuwenhuizen et al., 2011).

Impulsivity as a key characteristic for mental disorders associated with offending

Individuals with mental illness tend to exhibit inadequate coping mechanisms in response to stressful situations. Their behavior is often times rash and impulsive and can, in some cases, lead to acting-out behavior with significant negative consequences in the long term, such as the use of violence and committing criminal acts (Samuels, 2011; Pompili, Carlone, Silvestrini,

& Nicole, 2017). Most of the disorders commonly found in forensic psychiatric patients are characterized by high levels of impulsivity. For example, ADHD is characterized by "a persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning" (DSM-5, APA, 2013, p. 123). Significantly elevated impulsiveness is also found in violent offenders with schizophrenia (Enticott, Ogloff, Bradshaw, & Fitzgerald, 2008), whereas in antisocial personality disorder, a "long term pattern of […] impoverished moral sense or conscience, as well as a history of crime, legal problems, or impulsive and aggressive behavior" is a diagnostic criteria (DSM-5, APA, 2013, p. 866). Borderline personality disorder is characterized by a "pervasive pattern of instability of interpersonal relationships, […] marked by impulsivity beginning by early adulthood and present in a variety of contexts" criterion (DSM-5, APA, 2013, p. 872). In these contexts, impulsive behavior can possibly be harmful to oneself and/or others and has been associated with aggression or criminal behavior and risk-taking behavior (Black, Serowik, & Rosen, 2009; Verdejo-Garcia, Lawrence, & Clark, 2008).

Impulsivity can be defined as a dysfunctional personality trait, resulting in a tendency for an individual to display behavior that is performed with little or inadequate forethought and little consideration for consequences of the own behavior (e.g., Caswell, Bond, Duka, & Morgan, 2015; Evenden, 1999). It is increasingly seen as a multifaceted construct, which has been extensively studied in developmental and personality psychology. Impulsivity influences information processing at various stages (Clark, Robbins, Ersche, & Sahakian, 2006), and while there is an ongoing debate in the literature about the number and exact nature of different aspects of impulsivity, the following aspects have been identified as key elements of impulsivity: 1) response initiation, defined as responding before complete processing of a stimulus has occurred (Dougherty et al., 2009), which can sometimes also be called reflection impulsivity (Caswell et al., 2015), 2) response inhibition, a failure to inhibit a prepotent response (Dougherty et al., 2009), also labelled 'motor impulsivity' (Caswell et al., 2015), and 3) reward sensitivity, responses that favor short-term positive outcomes despite negative consequences in the long term (Dougherty et al., 2009). In dual-processing models, behavior is seen as the result of two qualitatively different processes, where impulsive (associative) processes compete against reflective processes (Wiers, Ames, Hoffmann, Krank, & Stacey, 2010; Stacy & Wiers, 2010). These dual-processing models also resemble neurocognitive models of impulsivity, where impulsive behavior is viewed as stemming from a failure of prefrontal cortex systems ('top down-systems') (Volkow, Fowler, & Wang, 2003), that, in healthy individuals, regulate 'bottom-up' urges of immediate reward (Stevens et al., 2014) generated in the limbic structures such as amygdala (Kulacaoglu & Kose, 2018; Siever, 2008). An individual's response to an immediate reward is also the result of a learning experience, where the association with a certain stimulus is valued in terms of its motivational impact (Wiers et al., 2010), determining the positive or negative reinforcement of a stimulus (Boog, Goudriaan, van de Wetering, Deuss, & Franken, 2013).

Differences between individuals regarding the positive reinforcing impact of a stimulus is called 'reward sensitivity', and determines the strength of an individual's urge to approach a certain stimulus (Boog et al., 2013; Wiers et al., 2010). Individuals high in 'reward sensitivity' are more likely to pay attention to and subsequently pursue reinforcing stimuli (Gullo & Dawe, 2008). While an individual's tendency to pursue a stimulus is also influenced by environmental factors such as family and peers (Gullo & Dawe, 2008), there is a lot of evidence in the scienti-fic literature about the crucial impact of adolescence in the manifestation of reward sensitivity, and

subsequently, cognitive (dis-)inhibition in response to reward (Gullo & Dawe, 2008). Adolescence therefore can be seen as a period of heightened risk to engage in impulsive, and possibly harmful behavior that has long lasting effects for later life. Associations between elevated levels of impulsivity during childhood and early adolescence, and a heightened risk to develop substance abuse problems in adulthood have been observed (Hentges, Shaw, & Wang, 2017). Subsequently, for disorders high in impulsivity, increased prevalence of SUD is rather common (Machielsen et al., 2012; Simpson, Grimbos, Chan, & Penney, 2015; Van Nieuwen-huizen et al., 2011).

Impulsivity and its relation to substance use disorder

Substance use disorder can be seen as a chronic condition of biopsychosocial nature that results in serious impairments in cognition and behavior (Sokhadze, Cannon, & Trudeau, 2008). When moving from recreational to compulsive drug use, the use of an addictive substance is continued despite the negative consequences of prolonged drug abuse. Poor response control is associated with rapidly escalating drug use, where control over drug intake is lost and drug use starts to become compulsive (Perry & Carroll, 2008). The urge for using is associated with tension, dysphoria and other negative states (Weddington et al., 1990), which can only be relieved by continuing intake of the addictive substance. Drug use then provides immediate reinforcement (Verdejo-Garcia et al., 2008), despite the long-term negative effects for almost all aspects of a person's life (De Wit & Richards 2004; Madden, Petry, Badger, & Bickel, 1997). High levels of impulsivity are strongly associated with the development, maintenance and relapse in substance abuse and addiction (e.g., Jentsch & Taylor, 1999; Volkow et al., 2003), and alcohol, stimulant, and opioid abusing individuals tend to have higher levels of impulsivity as compared to non-abusing controls (Loree, Lundahl, & Ledgerwood, 2015). Highly impulsive patients also tend to experience symptoms of withdrawal more seriously than less impulsive patients, as they report higher scores of craving for substances than patients with lower impulsivity scores (Joos et al., 2013), making them even more prone for relapse. Addictive substances may increase impulsivity levels, as a structural state of reduced inhibitory control due to substance abuse leads to long-lasting neurocognitive and neurophysiological changes (Perry & Carroll, 2008).

Yet, the exact nature of the causal association between heightened levels of impulsivity and SUD is still highly debated in scientific literature (Jentsch et al., 2014). Most likely, a predisposition for developing substance abuse problems, heightened levels of impulsivity, and further detrimental effects of addictive substances on response inhibition are strongly interconnected and cannot be viewed separately (Jentsch & Taylor, 1999; Lyvers, 2000). See Figure 1 for a graphical display. In recent years, studies have explored the common characteristics between impulsivity and SUD, and it is proposed that these two concepts stem from the same imbalance between neurocognitive bottom-up and top-down systems as already explained above (Bechara, 2005; Heatherton & Wagner, 2011; Tomko, Bountress, & Gray, 2016). In SUD, symptoms of dependency usually stem from bottom-up systems, with craving for substances - the urge to administer a drug - signaling the need for immediate reinforcement (Franken, 2003). Failure to suppress impulsive behavior can be seen as deriving from dysfunctional bottom-up systems, which overrule more reflective top-down systems in favor of immediate reward (Bechara, 2005; Stevens et al., 2014; Volkow et al., 2003). The interaction between these two neurocognitive processes resembles the dual-processing model mentioned above, which views impulsive behavior as the outcome between impulsive and more reflective processes (Wiers et al., 2010).

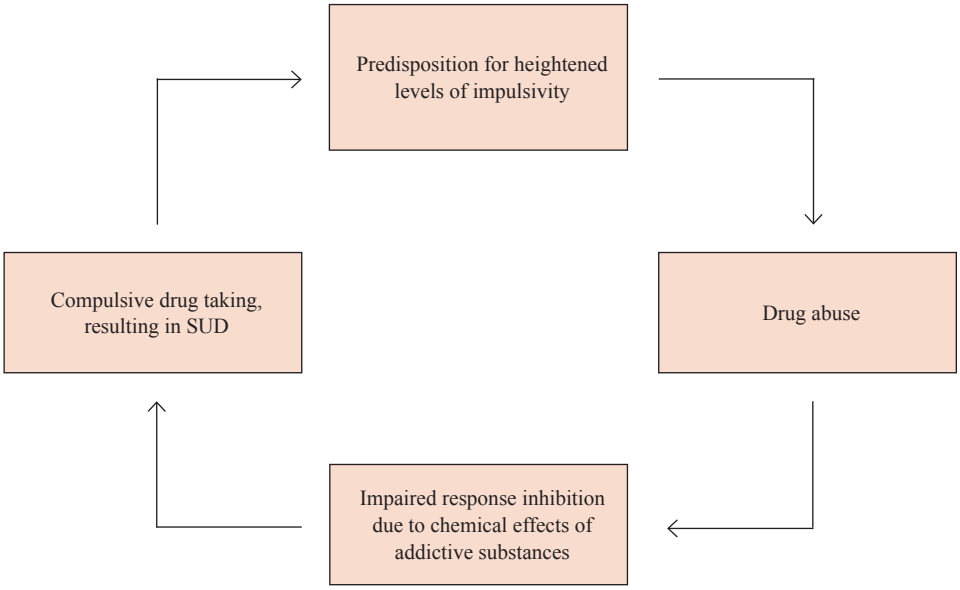


Figure 1. High levels of impulsivity are linked to the development and maintenance of substance abuse problems.

Treatment for forensic psychiatric patients with SUD

Once individuals seek treatment for substance abuse problems, treatment success is seriously hampered by high level of impulsivity (e.g., Charney, Zikos, & Gill, 2010; Van der Veeken, Lucieer, & Bogaerts, 2016). For forensic psychiatric patients especially, the maintenance of substance abuse poses risk for treatment failure. Drug abuse is a strong predictor of violent behavior, and subsequent violent criminal recidivism (Duke, Smith, Oberleitner, Westphal, & McKee, 2018; MacDonald, Erickson, Wells, Hathaway, & Pakula, 2008). The relationship between substance abuse, crime and violence has been established across a wide range of addictive substances, as well as types of mental disorder, such as psychotic disorders (Swanson et al., 2002) or personality disorders (e.g., Paim Kessler et al., 2012). High levels of impulsivity predict early relapse and increase chances of premature termination of substance abuse treatment (Charney et al., 2010). Poor treatment outcomes in these patients have been found across the literature, regardless of type of substance abuse (Van der Veeken et al., 2016). Given that the primary aim of treatment of forensic psychiatric patients is the prevention of violent criminal recidivism, substance abuse poses a substantial threat to achieve this aim. Hence, adequate treatment modalities for these highly impulsive individuals with substance abuse are much needed.

Treatment of forensic psychiatric patients faces many challenges. Patients with low treatment compliance, lack of problem insight, and risk for aggressive outbursts provide challenges for successful treatment of these patients residing in forensic facilities. Common methods of evidence-based therapy consist of Cognitive Behavioral Therapy (CBT), Schema Focus Therapy (SFT), medication, and participation in a therapeutic environment with well-specified rewards

and sanctions, which intent to help promote self-control, responsibility and thereby behavioral change (Welsh, Zajac, & Bucklen, 2013). Teaching patients to increase the use of attention to actions and goal-directed behavior is thought to reduce impulsivity and prevent relapse into drug abuse (Crews & Boettiger, 2009). However, effect sizes for prison-based substance abuse programs are usually small (e.g., Pearson & Lipton 1999; Magill & Ray, 2009). Therefore, additional treatment methods are needed in order to increase the chances for successful treatment outcomes. Neurofeedback could be a suitable intervention for forensic psychiatric patients. Neurofeedback is in its basics non-verbal and relies on the principles of operant condition, making it a suitable treatment intervention for a wide range of patient populations. Some studies have shown promising results for the reduction of impulsivity through means of neurofeedback (e.g., Fuchs, Birbaumer, Lutzenberger, Gruzelier, & Kaiser, 2003).

EEG-Neurofeedback: Historical overview

In the 1920's, Hans Berger was the first to measure electroencephalographic (EEG-)activity on the human scalp (Demos, 2005). He discovered that different mental states coincide with distinct EEG-activity that are distinguishable from one another. For example, Berger found that bursts in the alpha frequency band (7.5-12 Hz) were related to wakeful relaxation whereas EEG-activity in the beta frequency band (12-20 Hz) was related to the process of focusing attention and mental alertness (Demos, 2005). Correspondingly, Berger also believed that abnormalities in the EEG reflected clinical disorders (Criswell, 1995; Cantor, 1999; as cited in Demos, 2005). Since then, this notion has accumulated much evidence, and it is now widely accepted that deviant brain frequencies underlie mental disorders as well as their link to harmful behavior. Nowadays, electroencephalographic spectral analysis is frequently used to distinguish healthy controls from individuals with mental illness. For example, in ADHD, magnitude deviations in the theta (3.5-7.5 Hz) and beta frequency bands are thought to underlie symptoms of hyperactivity and/or impulsivity (Arns, Heinrich, & Strehl, 2014). The so-called theta/beta ratio, where theta activity is increased and beta activity is decreased as compared to healthy controls, has shown to have a sensitivity (the proportion of patients that are correctly identified as having the disorder) of 86%, and a specificity (the proportion of healthy individuals that are correctly identified as such) of 98% for identifying someone with ADHD (Monastra et al., 1999). In SUD, alterations in magnitude of specific EEG-frequencies vary by type of substance-dependency, but can resemble the alterations found in ADHD, with deviations often found in the theta, alpha, and beta frequencies (Sokhadze et al., 2011). In SUD, neurophysiological alterations are hypothesized to contribute to symptoms of substance dependency such as over-attention to drug-cues, lack of inhibitory control, loss of control over drug intake and drug craving (Dackis & O'Brien, 2001; Volkow et al., 2003). EEG-alterations are also found in cluster B personality disorders such as antisocial or borderline personality disorder, where an increase of slow wave activity, specifically within the delta (0.5-3.5 Hz) and theta frequency bands has been observed (De la Fuente, Tugendhaft, & Mavroudakis, 1998; Reyes & Amador, 2009). The increase in slow waves has been linked to violent and aggressive behavior in male psychiatric inpatients, independent of patients' current medication or treatment duration (Convit, Czobor, & Volavko, 1991).

Since Berger's discovery of coinciding mental states and distinct EEG-activity, it has also been established that humans are able to willingly control brain frequencies through reinforcement (e.g., research by Joseph Kamiya (1963) on alpha enhancement; or the work of Budzynski

(1999), as cited in Demos, 2005) on theta enhancement. See for an overview Demos, 2005). Even more so, willingly controlling EEG-frequencies has been shown to also affect behavior. As with many scientific discoveries, the discovery of clinical implications of altering EEG-frequencies was done partly by accident. In 1968, Barry Sterman conducted experiments on the trainability of the sensorimotor rhythm (SMR, 12-15 Hz) in cats (Wyricka & Sterman, 1968). Ten cats were rewarded every time they increased their SMR activity. However, as financial means for scientific research were scarce, these cats were also used for another experiment for NASA, where rocket fuel was injected in cats to study its effect on the development of seizures. Surprisingly, the cats that had previously been trained to increase SMR activity were not developing any seizures, as opposed to the cats that were not trained to increase SMR activity. With that, the notion of what was then called biofeedback was born. This technique applies means of operant conditioning to teach patients to change cortical neuronal activity over time (Sokhadze et al., 2011). EEG-activity is measured and information about these measurements is fed back to the patient through simple video-games. The video-games display changes in EEG-parameters, and the patient learns to control the video-games by employing mental strategies. Thereby, patients learn to inhibit or reinforce these EEG-parameters, which can lead to the normalization of abnormal EEG-activity (Scott, Kaiser, Othmer, & Sideroff, 2005).

Since then, thousands of studies have investigated the effects of neurofeedback on clinical symptoms and behavior (Rogala et al., 2016). One of the earliest clinical effects in humans with neurofeedback therapy was found in participants with ADHD. Lubar and Shouse (1976) applied SMR neurofeedback training in a child with (what is now known as) ADHD, and found that an increased activity of SMR was associated with reduced motor impulsivity, as well as improvements on behavioral measures such as hyperactivity and distractibility. Other landmark studies include the study on the effects of neurofeedback training in Vietnam veterans who had a dual diagnosis of alcohol dependency and posttraumatic stress disorder (PTSD; Peniston & Kulkosky, 1991). Peniston and Kulkosky (1991) employed neurofeedback training (known now as the 'Peniston Protocol) in these patients and found clinical symptom improvements that were superior to traditional medication treatment.

Neurofeedback in forensic psychiatric patients with substance abuse

Since these early studies, different neurofeedback training protocols have been established, where specific EEG-frequencies are enhanced (or 'up-trained'), while others are inhibited (or 'down-trained'), based on Berger's notion that normalization of aberrant EEG-activity can change abnormal psychological states. These training protocols are used for many different clinical symptoms, as well as in many different patient populations. For the reduction of high levels of impulsivity, neurofeedback protocols typically focus on the reduction of slow wave activity such as theta, and enhancement of faster activity such as beta or SMR. Elevated theta activity has been consistently linked with higher levels of impulsivity across various subject populations (e.g., Bresnahan & Barry, 2002; Hermens, Kohn, Clarke, Gordon, & Williams, 2005; Stenberg, 1992). Increased SMR activity is seen when humans try to inhibit a motor response, and neurofeedback training where the SMR activity has been up-trained has been found to facilitate thalamic inhibitory mechanisms (Sterman, 1996). In ADHD, neurofeedback protocols therefore usually aim at targeting the overrepresentation of slow wave activity such as delta (0.5-3.5 Hz) and theta (3.5-7.5 Hz), and the underrepresentation of faster waves like beta (12-20 Hz) or the SMR

frequency (12-15 Hz) (Arns et al., 2014; Fuchs et al., 2003). The alterations in theta, beta and SMR frequency bands have also been observed in patients with substance abuse (Sokhadze et al., 2011). However, typical neurofeedback protocols for the treatment of addiction employ an alpha/theta neurofeedback first, which is then followed by the same theta/SMR protocol that is also used in ADHD (also known as the Scott-Kaiser modification of the Peniston Protocol; Scott et al., 2005). Although this protocol has shown promising results in reducing symptoms of substance abuse in patients with SUD, such as craving (e.g., Arani, Rostami, & Nostrabadi, 2010; Sokhadze et al., 2014), it can be argued that for any substance abuse treatment to be successful, dysregulation of impulse control should be a prime candidate, as this dysregulation places individuals at risk for poor response to SUD treatment (Loree et al., 2015; Tomko et al., 2016; Stevens et al., 2014). Usually, patients in substance abuse treatment are well aware that continuing to abuse substance has negative consequences, but they are nevertheless unable to control drug intake due to reduced inhibitory control. A theta/SMR neurofeedback training protocol aimed at reducing impulsivity might help these patients to inhibit dysfunctional responses to drug cues and therefore they may be more able to resist drug intake, resulting in beneficial effects on symptoms of substance abuse. Also, given that impulsivity has been shown to be related to severity of experienced drug craving, a theta/SMR neurofeedback training could also help patients deal with this key symptom of SUD (Moeller et al., 2001).

Assessing the efficacy of neurofeedback training

Still, neurofeedback training is not commonly applied in forensic inpatient treatment facilities. Treatment supervisors are hesitant to apply this treatment modality into common practice (Van Outsem, 2011). Specifically, there are only a limited number of studies describing effects of neurofeedback training in criminal populations (e.g., Konicar et al., 2015; Martin & Johnson, 2005; Smith & Sams, 2005; Quirk, 1995; see for overview Fielenbach, Donkers, Spreen, Visser, & Bogaerts, 2018b). The hesitancy of treatment supervisors to integrate neurofeedback training into standard treatment programs may be partially due to the fact that, even decades of neurofeedback research and the promising results some studies have shown, there is an ongoing debate about which factors exactly are associated with beneficial outcomes after training. There is great variation between studies when it comes to applied neurofeedback training protocols, number of sessions applied, and time intervals in which the training sessions are scheduled. In studies with ADHD, neurofeedback training often includes up to 40 sessions (Carmody, Radvanski, Wadhwani, Sabo, & Vergara, 2001; Monastra, Monastra, & George, 2002). In substance dependent patients, promising results have been found after only 12 sessions (Horrell et al., 2010), whereas others have employed 30 sessions (Arani et al., 2010).

The efficacy of neurofeedback training can be measured in two complementary ways: 1) Through changes at the neurophysiological level, i.e., normalization of deviant brain wave patterns, or increase/decrease of EEG-activity in particular frequency bands post-training, and 2) through improvements in behavior, i.e., clinical symptoms (Rogala et al., 2016). It can be argued that, for the training to be efficient, one cannot occur without the other.

The first way of assessing the effectiveness of neurofeedback training can be described with the term 'EEG-learning'. EEG-learning indicates whether patients have been able to learn how to influence the targeted EEG-activity. Zoefel, Huster and Herrmann (2011) describe this as 'trainability', where participants show "spectral effects within the trained frequency bands *caused*

by the training." In recent years, studies have focused more and more on the different ways patients learn to control EEG-activity, and different patterns of learning have been observed. In studies with healthy participants, learning performance showed to be highest in the beginning of training sessions, but then stabilized and did not increase any further (e.g., Ros et al., 2009; Dekker, Sitskoorn, Denissen, & Van Boxtel, 2014). In patient populations, ADHD patients for instance showed good neurofeedback performance during the first phase of training as indicated by an improvement in theta/beta ratio, but then stagnated in performance before increasing performance again by the end of the training (Bakhshayesh, Hänsch, Wyschkon, Rezai, & Esser, 2011). Contradictory, Bink, van Nieuwenhuizen, Popma, Bongers, and van Boxtel (2015) found that adolescents with ADHD needed more time to learn to control theta activity and were better able to suppress this activity by the end of the training than during the first sessions.

Interindividual differences with regard to EEG-learning have also been observed when it comes to different EEG-frequencies. Several studies suggest that patients find certain EEG-frequencies easier to control than others. For instance, in a study by Janssen et al. (2017), beta frequency increased linearly over the course of training, whereas participants failed to change theta activity. In a study by Doppelmayr and Weber (2011), participants succeeded in regulating SMR activity, but failed to regulate the theta/beta ratio.

When adhering to the criteria for evaluating the efficacy of neurofeedback training as stated above, improvements on a neurophysiological level should be related to improvements on a behavioral level. Some studies suggest that better performance during neurofeedback training also results in more improvements in clinical symptoms. DeBeus and Kaiser (2011) report a significant positive correlation between participants' ability to improve EEG-regulation and the degree of improvements in ADHD symptoms. In a study by Drechsler et al. (2007), good neurofeedback training performance was related to greater improvements on hyperactivity and impulsivity in ADHD children. In the only study known so far that applied neurofeedback in a group of criminal offenders and also assessed results on a neurophysiological level, larger improvements on behavioral measures such as physical aggression and aggression inhibition were linked with better neurofeedback training performance (Konicar et al., 2015).

However, there is also a group of participants that fail to learn the principles of EEG-regulation altogether, and therefore show no changes on a neurophysiological level immediately after the last training session or at a later follow-up. These patients have been named 'non-responders' (Enriquez-Geppert et al., 2013; Zoefel et al., 2011). Investigations into neurofeedback learning have shown that in some studies as many as 50% of participants can be classified as non-responders (e.g., Doehnert, Brandeis, Staub, Steinhausen, & Drechsler, 2008). Even in studies with healthy participants, non-responders are still found (e.g., Hanslmayer, Sauseng, Doppelmayr, Schabus, & Klimesch, 2005; Weber, Köberl, Frank, & Doppelmayr 2011). In recent years, the term 'brain-computer illiteracy' has been termed for the failure to gain control over cortical activity (Zuberer, Brandeis, & Drechsler, 2015). To date, it is still unclear which mechanisms are responsible for differences in participants' ability to learn EEG-regulation. Apart from some methodological and technical aspects of EEG-research, it has also been proposed that variables such as mood, motivation or the distraction of the participant may play a role in participants' performance (Zuberer et al., 2015).

Adhering to the criteria stated above, non-responders should not show any improvements in clinical symptom post-training. However, there are studies that report improvements on a behavioral level

even though no significant changes were observed in EEG-activity post-neurofeedback training (e.g., Arns, Drinkenburg, & Kenemans, 2012; Schönenberg et al., 2017). The presence of clinical symptom improvements without any significant changes at the neurophysiological level post-training raises the notion of possible placebo effects of neurofeedback training. Other mechanisms must be in place when it comes to clinical symptom improvement. A necessary first step to show that clinical improvements can be attributed to successful regulation of cortical activity therefore is to demonstrate that learning of EEG-regulation has occurred during neurofeedback training (Gruzelier, Egner, & Vernon, 2006; Zuberer et al., 2015).

To date, it remains unclear what the effects of a theta/SMR neurofeedback training protocol are not only on levels of impulsivity, but also on symptoms of SUD such as levels of drug craving and actual drug use in forensic psychiatric patients. There are basically no studies that have investigated the effects of such a training protocol in forensic populations in which heterogeneity of clinical diagnoses and symptoms is especially pronounced. Treatment of forensic psychiatric patients with dual-diagnosis should integrate different multidisciplinary treatment approaches, which focus on the interactive nature of SUD and other mental disorders (Horsfall, Cleary, Hunt, & Walter, 2009). If efficient, a neurofeedback training protocol aimed at reducing high levels of impulsivity could be a valuable addition to standard treatment modalities.

The current study

This study is set in the FPC Dr. S. van Mesdag, a forensic psychiatric center (FPC) in Groningen, The Netherlands. Patients in this maximum security treatment facility are male forensic psychiatric patients with at least one mental disorder according to DMS-IV-TR (APA, 2000). Next to other mental disorders, about 70% of patients are diagnosed with substance abuse problems. Patients are considered high-risk for reoffending, and are treated on behalf of the state in a multidisciplinary environment. The aim of the treatment is to reduce clinical symptoms that are considered high-risk for reoffending, and to integrate patients back into society by the means of stepwise furlough and expansion of liberties.

The study investigates the effects of a theta/SMR neurofeedback training protocol in addition to treatment as usual in participants from the treatment facility described above. More specifically, it investigates to what extent a theta/SMR neurofeedback training intervention reduces levels of impulsivity and symptoms of substance dependency, such as drug craving and drug use. It will focus on two main components for the application of neurofeedback training in forensic psychiatric patients: 1) Whether these patients are able to learn the regulation of EEG-activity, and 2) whether EEG-activity regulation through a theta/SMR neurofeedback training leads to a decrease in levels of impulsivity and symptoms of drug addiction. Effects of a theta/SMR neurofeedback training protocol on a group level will be investigated with a randomized controlled trial (RCT).

To investigate the clinical effects of this intervention more closely, a sham-controlled clinical case series will also be applied. In clinical case studies, more information can be gathered about the timeframe in which clinical significant changes can be achieved by monitoring individual patient(s) more closely. This approach also allows for the detection of interpersonal differences in response to the intervention, which are not revealed with between-group comparisons typically assessed with RCT designs. By definition, SUD treatment that matches an individual's maintaining factors for dependency should be more effective than a treatment that does not consider these factors (Tomko et al., 2016).

Outline of this thesis

Chapter 2 provides a systematic review of previous studies on neurofeedback training for mental disorders commonly found in forensic psychiatric patients. The article discusses the implications of these studies for the applicability of neurofeedback training in forensic psychiatric patient populations.

Chapter 3 presents the research protocol for the current study, where neurofeedback training is applied in male forensic psychiatric patients with SUD.

Chapter 4 reports the results for a subset of the patients who participated in neurofeedback training. It was investigated whether forensic psychiatric patients diagnosed with SUD were able to learn to regulate neurophysiological activity through a theta/SMR neurofeedback and to what extent magnitude changes in these frequency bands are related to changes in levels of impulsivity. Criteria for qualifying patients as responders were established and scores on impulsivity measures and changes in level of craving over time were assessed.

Chapter 5 presents the results of the first RCT investigating the effects of theta/SMR neurofeedback training in forensic psychiatric patients. Main outcome measurements reported are levels of impulsivity, craving, and actual drug intake.

Chapter 6 describes the results of a sham-controlled series of clinical case studies, where two cases employed a theta/SMR neurofeedback protocol and two cases employed sham neurofeedback. Self-report level of impulsivity and craving were assessed.

The **final chapter** will provide a general discussion of the main findings of this thesis. Limitations of the current study will be discussed, as well as recommendations for future studies.

Chapter 2

Neurofeedback training for psychiatric disorders associated with criminal offending: a review

Published as: Fielenbach, S., Donkers, F. C. L., Spreen, M., Visser, H. A., & Bogaerts, S. (2018). Neurofeedback training for psychiatric disorders associated with criminal offending: A review. Frontiers in Psychiatry, 8. doi:10.3389/fpsyt.2017.00313

Abstract

Effective treatment interventions for criminal offenders are necessary to reduce risk of criminal recidivism. Evidence about deviant EEG-frequencies underlying disorders found in criminal offenders is accumulating. Yet, treatment modalities such as neurofeedback are rarely applied in the forensic psychiatric domain. Since offenders usually have multiple disorders, difficulties adhering to long-term treatment modalities, and are highly vulnerable for psychiatric decompensation, more information about neurofeedback training protocols, number of sessions, and expected symptom reduction is necessary before it can be successfully used in offender populations. Studies were analyzed that used neurofeedback in adult criminal offenders, and in disorders these patients present with. Specifically aggression, violence, recidivism, offending, psychopathy, schizophrenia, ADHD, substance use disorder, and cluster B personality disorders were included. Only studies that reported changes in EEG-frequencies post-treatment (increase/decrease/no change in EEG amplitude/power) were included. Databases PsychInfo en Pubmed were searched for the period 1990-2017 according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), resulting in a total of 10 studies. Studies in which neurofeedback was applied in ADHD (N=3), substance use disorder (N=3), schizophrenia (N=3) and psychopathy (N=1) could be identified. No studies could be identified for neurofeedback applied in cluster B personality disorders, aggression, violence or recidivism in criminal offenders. For all treatment populations and neurofeedback protocols, number of sessions varied greatly. Changes in behavioral levels ranged from no improvements to significant symptom reduction after neurofeedback training. The results are also mixed concerning post-treatment changes in targeted EEG-frequency bands. Only three studies established criteria for EEG-learning. Implications of the results for the applicability of neurofeedback training in criminal offender populations are discussed. More research focusing on neurofeedback and learning of cortical activity regulation is needed in populations with externalizing behaviors associated with violence and criminal behavior, as well as multiple comorbidities. At this point, it is unclear whether standard neurofeedback training protocols can be applied in offender populations, or whether QEEG-guided neurofeedback is a better choice. Given the special context in which the studies are executed, clinical trials, as well as single-case experimental designs, might be more feasible than large double-blind randomized controls.

Rationale

Criminal offenders are a challenging patient group when it comes to adequate treatment interventions. This patient group exhibits externalizing behavior and usually suffers from schizophrenia, attention-deficit hyperactivity disorder (ADHD), substance use disorder (SUD), and cluster B personality disorders, with high comorbidity rates (Van Nieuwenhuizen, Bogaerts, Ruijter, Bonges, Coppens, 2011; Woicik, Van der Lem, Sijtsema, & Bogaerts, 2017). In order to prevent the risk of criminal recidivism and the suffering for potential victims, effective treatment interventions are necessary.

In the last three decades, electroencephalographic (EEG) based neurofeedback training has been increasingly used in the treatment for various psychiatric disorders. Neurofeedback is an operant conditioning training aiming to improve brain activity, as well as to improve cognitive, behavioral, and emotional self-regulatory skills by learning patients how to control abnormal psychological states such as inattention and stress (Gunkelman, & Johnstone, 2005; Hammond et al., 2011). Previous studies have accumulated much evidence about deviant EEG-frequencies underlying disorders commonly found in criminal offenders that could be a target for neurofeedback training. Still, to date neurofeedback is hardly used in the forensic psychiatric domain (e.g., Van Outsem, 2011).

In ADHD, common EEG-deviations reported in the literature concern the overrepresentation of slow frequencies like delta (0.5-3.5 Hz) and theta (3.5-7.5 Hz), with reduced amplitudes of faster waves like beta (12-20 Hz) or the sensorimotor rhythm (SMR, 12-15 Hz). The cortical slowing is hypothesized to underlie symptoms such as inattention, impulsivity, and inhibitory control (Van Doren et al., 2017). There is an ongoing debate in the EEG-based ADHD literature about whether these deviations are more common in children presenting with ADHD rather than adults, or whether there is a natural remission with aging of ADHD patients of their immature EEG-activity (Mann, Lubar, Zimmerman, Miller, & Muenchen, 1992). Other deviations reported include the Event-Related Potential (ERP) markers of response preparation, specifically the Contingent Negative Variation (CNV) component of the Slow Cortical Potential (SCP). Aberrant CNV patterns have been related to a reduction of attention, inhibition, and cognitive control (Barry, Johnstone, & Clarke, 2003).

While ADHD is overrepresented in forensic psychiatric patients (Woicik et al., 2017), deviant EEG-frequencies have been less studied in other psychiatric disorders commonly found in criminal offenders. In schizophrenia, EEG-deviations have been observed in as many as 60% of patients (Small et al., 1984; Ellingson, 1954). Abnormal EEG-activity reported include decreased alpha activity, increased beta activity (Fenton, Fenwick, Dollimore, Dunn, & Hirsch, 1980; Merrin, & Floyd, 1992; Surmeli, Ertem, Eralp, & Kos, 2012), and reduced amplitudes of the CNV, reflecting disturbed information processing (Schneider et al., 1992). In substance-use disorder, chronic substance abuse has been hypothesized to produce neural changes leading to a structural state of disinhibition and impulsivity (Bates, Bowden, & Barry, 2002; Jentsch, & Taylor, 1999; Lyvers, 2000). EEG-deviations found in subjects with a history of prolonged substance abuse include alterations in theta, alpha and beta frequency bands (Arani, Rostami, & Nostrabadi, 2010; Sokhadze, Stewart, Tasman, Daniels, & Trudeau, 2014). These deviations in EEG-frequencies are hypothesized to underlie classic symptoms of SUD, such as craving, over-attention to drug-cues, feelings of restlessness, and loss of impulse

control (Charney, Zikos, & Gill, 2010; Dackis, & O'Brian, 2001; Volkow, Fowler, & Wang, 2003). In antisocial personality disorder, increased slow wave activity has been observed (Reyes, & Amador, 2009), this has also been reported in borderline personality disorder (De la Fuente, Tugendhaft, & Mavroudakis, 1998; Tanahashi, 1988). This increase in slow wave activity has been linked to violence and aggressive behavior (Convit, Czobor, Volovka, 1991). In psychopathy, a personality construct which has many similarities with antisocial personality disorder (Konicar et al., 2015), dysregulation of SCP has been linked to poor anticipatory planning, self-regulation, and formation of stable expectancies (Flor, Birbaumer, Hermann, Ziegler, & Patrick, 2002; Birbaumer, Elbert, Canavan, & Rockstroh, 1990; Forth, & Hare, 1989; Jutai, & Hare 1983).

Although neurofeedback has been considered as a possible treatment intervention for antisocial and violent behavior (e.g., Van Outsem, 2011; Raine, 1996), not many studies have been conduc-ted in offender populations, although several studies indicate that improvements were found after neurofeedback training (e.g., Martin & Johnson, 2005; Smith & Sams, 2005; Quirk, 1995), as for instance, in aggressive behavior and attention (Martin & Johnson, 2005), or even in recidivism rates (Quirk, 1995). However, these studies did not report EEG-changes in training parameters post-treatment, so no conclusions can be drawn about how these findings are related to changes at a neurophysiological level.

Some studies suggest that greater response to neurofeedback training in terms of more successful cortical regulation will result in higher clinical improvements (Van Doren et al., 2017). Surprisingly, many neurofeedback studies determine the effectiveness of the training by reporting improvements in behavioral symptoms only. Whether these behavioral changes are associated with changes in cortical brain activity is not examined (e.g., Duric, Aßmus, & Elgen, 2014; Fuchs, Birbaumer, Lutzenberger, Gruzelier, & Kaiser, 2003). Therefore, it remains unclear how many patients actually responded to the training in terms of changes in EEG-activity. In addition, few studies report within-session and/or cross-session learning effects, and only focus on the pre- and post-intervention change, making it difficult to determine how many sessions were in fact necessary to reach the desired effects. Common neurofeedback protocols can range up to 50 sessions (e.g., Heinrich, Gevensleben, Freisleder, Moll, & Rothenberger, 2004; Scott, Kaiser, Othmer, & Sideroff, 2005), while there is also evidence suggesting that significant improvements can be achieved within as few as 15 sessions (Schönenberg et al., 2017). The number of neurofeedback sessions required to reach optimal training success is unclear, and whether more training sessions will actually lead to higher clinical improvements is still up for debate. Reporting changes in EEG-frequency bands after neurofeedback training seems a necessary first step in determining whether treatment success was related to the applied neurofeedback protocol. Zuberer, Brandeis, and Drechsler (2015) provide a useful review of studies that investigate learning of cortical activity in participants with ADHD, and also report some studies that show non-learning, in what they call 'brain-computer illiteracy' (Zuberer et al., 2015). Given that even studies with healthy participants have shown that about half of the participants were not able to learn cortical regulation through neurofeedback (Weber, Köberl, Frank, & Doppelmayer, 2011), it is to be expected that forensic patients with various comorbidities have more difficulties to actually learn the principles of neurofeedback. This may reduce chances to achieve beneficial clinical effects.

As forensic psychiatric patients usually present with multiple disorders (Woicik et al., 2017),

have difficulties adhering to long-term treatment modalities due to low levels of treatment motivation, and are highly vulnerability for psychiatric decompensation, it is important to investigate the feasibility of this intervention, before forcing a large number of sessions upon patients. More information about the type of neurofeedback training protocols, number of sessions, and expected symptom reduction is necessary.

Research question

This study aims to review studies that applied neurofeedback training in criminal offenders, taking into account the multiple disorders of these patients. As such, this review focusses on neurofeedback as an intervention for criminal offending, recidivism, reoffending, aggression, violence, and the following disorders associated with criminal offending: ADHD, schizophrenia, psychosis, all Cluster B personality disorders, psychopathy and substance use disorder. Only studies that examined whether or not neurofeedback led to changes in the trained EEG-treatment parameters were considered. Three factors contributing to the evaluation of neurofeedback training were assessed: 1) the type of neurofeedback protocol applied, 2) the number of sessions during which the neurofeedback protocol was applied, and 3) the change in neurofeedback training parameters.

Method

Study design

This review focused on single-electrode EEG-neurofeedback, and therefore excluded neurofeedback modalities such as inter-hemispheric bipolar EEG-neurofeedback, near-infrared spectroscopy (NIRS) neurofeedback or functional Magnetic Resonance Imaging (fMRI) neurofeedback. Studies in which EEG-neurofeedback was combined with other feedback modalities, such as EMG-biofeedback in the experimental condition were also excluded. Up until the end of the 1990's, EEG-biofeedback was the most common search term regarding neurofeedback (Arns, Heinrich, & Strehl, 2014). Therefore, EEG-biofeedback was included in the search terms. The following search terms were entered into the databases: neurofeedback or EEG-neurofeedback or EEG-biofeedback AND criminal offending, recidivism, reoffending, aggression, violence, psychopathy, schizo* or psycho* or psychosis or ADHD or attention-deficit or ADD or personality disorder or antisocial or narcissistic or borderline or addict* or substance use or substance abuse or substance dependen*. Only studies using adult participants (mean age >18) were included. As the major mental disorders most commonly associated with criminal recidivism are associated with problems in impulse control and aggression, neurofeedback or EEG-neurofeedback or EEG-biofeedback AND impulsivity or aggression were included. Change in EEG-parameters was defined as whether neurofeedback resulted in a change in EEG-frequency bands (increase or decrease in mean amplitude/power). Studies in which changes in EEG-training parameters were observed without highlighting the direction of the effect were excluded, as well as studies where the dependent variable was 'cortical activation' or related terms without further description of specific change in trained frequency bands.

Inclusion criteria:

1. The applied treatment was EEG-neurofeedback.
2. The study contained detailed information about number of sessions applied, neurofeedback protocol applied, and electrode position used.
3. The study provided detailed information about change in EEG-training parameters due to neurofeedback training.

Search Strategy

The search strategy consisted of two steps: First, databases were searched with the aforementioned terms. Electronic databases searched were PsychInfo and PubMed. Only English articles published from 1990 up until November 3rd of 2017 were taken into account. Book chapters, dissertations, letters to the editor and anecdotal case reports were not included. Studies in which neurofeedback protocols were tested on healthy individuals were also excluded, as well as articles describing training-effects on non-psychopathological features such as music performance. Articles resulting from the search strategy were scanned for relevance by screening titles and abstracts. Next, articles that seemed to meet inclusion criteria were examined more closely for fulfillment of all criteria. This step was done independently by two researchers (SF and HAV). If no agreement could be reached, an independent third party (FCLD) was asked in deciding whether or not the study had to be included. See Figure 1 for a flow diagram of selection of studies.

Results

The initial search resulted in 224 articles that were screened. Of these, 10 studies met the inclusion criteria. Table 1 lists all studies that meet the inclusion criteria and gives an overview of the employed neurofeedback protocol, characteristics of the control group, moments of measurement, targeted neuropsychological and behavioral effects, whether the study stated a criterion for defining learners and non-learners, as well as the reported results.

Although the search concentrated on studies concerning neurofeedback training for aggression, violence, recidivism, offending, psychopathy, schizophrenia, psychosis, Cluster B personality disorders, substance use disorder and attention-deficit disorder, only studies for schizophrenia, attention-deficit/hyperactivity disorder, and substance use disorder could be detected that met the inclusion criteria.

Attention deficit/ Hyperactivity Disorder

Three studies on ADHD were found that met the inclusion criteria (Arns et al., 2012; Mayer, Blume, Wyckoff, Brokmeier, & Strehl, 2016; Schönenberg et al., 2017). All studies used different neurofeedback protocols: Arns et al. (2012) employed a QEEG-guided feedback protocol, where enhancement/decrease in frequencies was based on deviations found in the QEEG at pre-treatment assessment. Mayer et al. (2016) employed a SCP-protocol, whereas Schönenberg et al. (2017) employed a theta/beta protocol. Applied number of sessions was approximately 30. All three studies reported significant clinical changes concerning ADHD symptoms, such as inattention, hyperactivity, impulsivity, and depressive symptoms, while

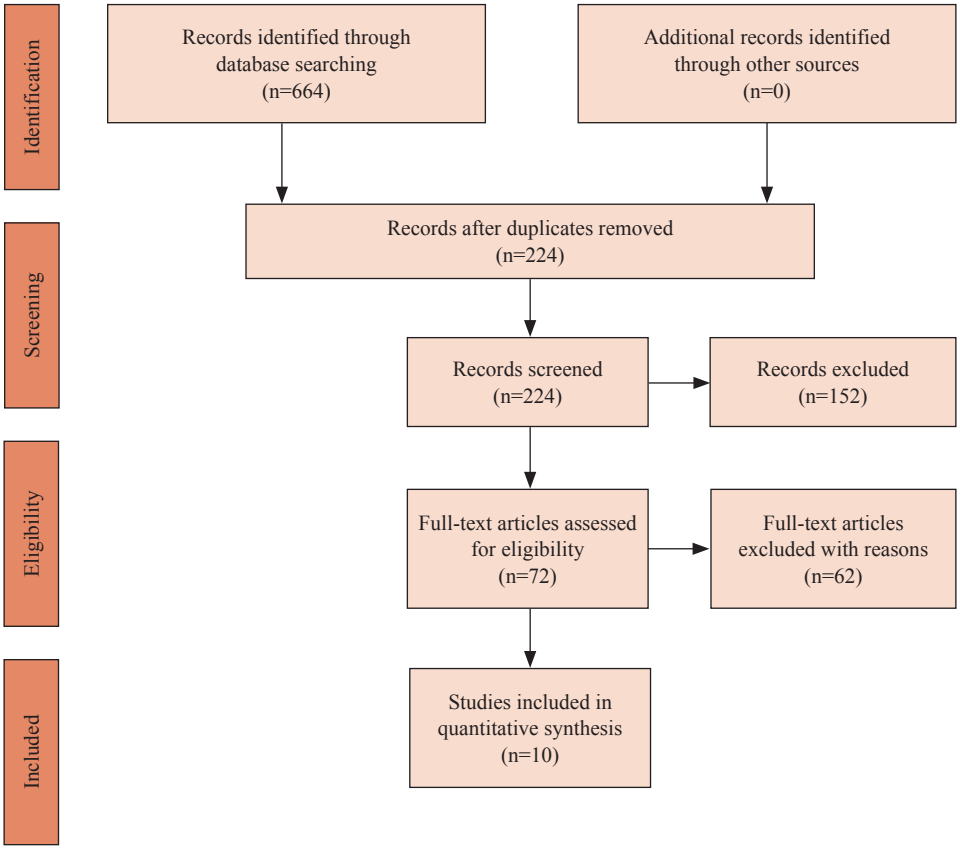


Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of selection of studies. Two articles included in the search results refer to the same study, so the flow chart does not count them twice.

changes in trained EEG-frequencies post-treatment were not significant or only by trend. In Schönenberg et al. (2017), no significant effect of time/treatment was found, whereas Mayer et al. (2016) report a trend towards significance concerning the desired increase of CNV amplitude. In Arns et al. (2012), a significantly decreased SMR power was found post-treatment in patients who underwent a SMR-training protocol, while the training was actually aimed at enhancing this frequency band. Only one of the studies actually linked the results found on a neurophysiological level to behavioral outcome measures. Arns et al. (2012) reported a significant correlation between anterior individual alpha peak frequency and the percentage of improvement on depressive symptoms post-treatment, suggesting that participants with a slower anterior alpha peak frequency improved less on comorbid depressive symptoms. Only the study by Schönenberg et al. (2017) employed a control group (sham neurofeedback and meta-cognitive therapy), and effects of neurofeedback training were not superior to effects found in the control group.

Substance Use Disorder

For SUD, three studies met the inclusion criteria (Arani et al., 2010; Horrell et al., 2010; Lackner et al., 2016). The studies employed three different types of protocols: A classic Peniston Protocol (alpha-theta neurofeedback) in alcohol dependent patients (Lackner et al., 2016), a Scott-Kaiser modification of the Peniston Protocol (alpha-theta training followed by a SMR-protocol) in opiate dependent patients (Arani et al., 2010), and a SMR-based protocol in cocaine abusers (Horrell et al., 2010). Number of sessions ranged from 12 to 30 sessions. In all studies, the investigated behavioral outcome measures did not only concern substance use itself, but also concerned related clinical symptoms such as broader psychopathology (e.g., the Symptom Checklist-90 (SCL-90) in the study by Arani et al., (2010) and the Brief Symptom Inventory (BSI) in the study by Lackner et al. (2016)), posttraumatic-stress syndrome related symptoms and depression scores (e.g., BDI in the study by Lackner et al., 2016 and Horrell et al., 2010). Post-treatment, positive effects were reported for some of the subscales of the SCL-90 (Arani et al., 2010) and depressive symptoms and level of stress (Horrell et al., 2010), whereas Lackner et al. (2016) found no significant behavioral changes except for an effect by trend in the sense of coherence, a concept strongly related to perceived mental health. Concerning primary symptoms of SUD, Arani et al., (2010) found a significant decrease of a number of subscales of a craving questionnaire (desire to use addictive substances, relief from withdrawal symptoms and anticipation of positive outcome), and Horrell et al. (2010) found a decrease in number of positive drug testing after neurofeedback training. Arani et al., (2010) and Horrell et al. (2010) also found significant effects in at least some of the EEG-frequency bands trained (delta, theta, alpha and SMR). Lackner et al. (2016) found a trend towards an increase in theta and alpha in absolute power bands, but the effects could not be found at six months follow-up assessment. However, participants' perceived control over EEG-activity, as well as anticipation of positive outcomes of training significantly, increased over the course of training.

Schizophrenia

Three studies could be identified that met the inclusion criteria for neurofeedback studies in patients with schizophrenia (Gruzelier, Hardman, Wild, & Zaman, 1999; Nan et al., 2017; Schneider et al., 1992). The studies by Gruzelier et al. (1999) and Schneider et al. (1992) employed SCP-neurofeedback at central electrode positions, whereas Nan et al. (2017) trained the individual alpha peak frequency in a single-subject design. Number of sessions ranged from 10 to 20, with the exception for Nan et al. (2017) who employed 12.5 hours of neurofeedback training within four consecutive days. Gruzelier et al. (1999) and Schneider et al. (1992) investigated whether patients were able to learn to control SCP. Gruzelier et al. (1999) found patients able to learn to control interhemispheric asymmetry, whereas Schneider et al. (1992) found schizophrenic patients to only achieve differentiation of feedback trials comparable to controls in the last three sessions of training. Only Nan et al. (2017) investigated effects on a behavioral level through a short-term memory test, which improved post-treatment, while results concerning change in EEG-frequencies post-treatment were only significant by trend.

Offending/Psychopathy

Only one study was found regarding neurofeedback training in a population of criminal offenders and adhered to our inclusion criteria. The study by Konicar et al. (2015) employed a 25-session

SCP-training protocol in a population of offenders with high scores on the Psychopathy Checklist-Revised (Hare, 2003). Behavioral outcome measures concerned clinical symptoms, such as aggression as well as behavioral approach/avoidance constructs. Post-treatment, there was a significant reduction in physical aggression measurements as well as in behavioral approach, while reactive aggression and aggression inhibition did not improve significantly.

EEG-learning

Only three out of ten studies established criteria for EEG-learning (Gruzelier et al., 1999; Mayer et al., 2016; Schneider et al., 1992). Gruzelier et al. (1999) differentiated between good and bad performers based on visual inspection of performance of training sessions when comparing the first five sessions with the last five sessions, and reported that good performers had lateral shifts about twice as large as average performers. In Schneider et al. (1992), learning success was defined as mean difference between required negativity increase and negative suppression and found that for patients, learning success took longer in time to manifest as compared to controls. Learning success correlated negatively with symptomatology at the beginning of the study, history of illness, and number of hospitalizations, implying that patients with a worse history of schizophrenic symptoms were less able to learn principals of neurofeedback training. The study by Mayer et al. (2016) was the only study that established criteria for EEG-learning and also investigated whether EEG-learning was related to changes in clinical symptoms. They reported a trend towards significance for higher ADHD symptom improvement in patients who could be classified as a 'neurofeedback-learner' (based on a participants' ability to differentiate between negativation and positivation in neurofeedback transfer conditions). The study by Arns et al., (2012) did not establish criteria for EEG-learning, but classified responders to neurofeedback training based on clinical symptom reduction. They found a response rate of 76% based on behavioral measures, with significant improvements on attention, impulsivity and comorbid depressive symptoms, but post-treatment EEG measurements were only available for six out of 21 patients. The results of the available EEG measurements indicated changes in training parameters in an opposite direction as expected, as shown by a decrease in SMR power post-treatment when actually SMR was up-trained. In the study by Konicar et al. (2015), the level of participants' SCP-differentiation was correlated with improvements on behavioral measures, indicating larger reductions in physical aggression, behavioral approach, reactive aggression and aggression inhibition, with greater SCP-differentiation indicating higher clinical improvements.

Risk for bias

Risk for bias in the selected studies was analyzed according to Cochrane standards of practice (Higgings & Green, 2017). Two reviewers (SF and HAV) independently scored the risk for bias and then reached consensus. See Figure 2 and 3 for an assessment of bias in the included studies. Risk for bias mainly stemmed from a lack of control conditions, lack of blinding, and incomplete outcome data.

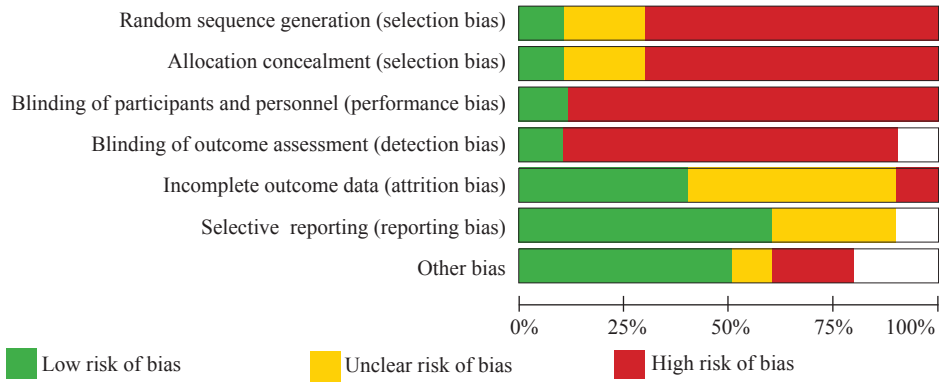


Figure 2: Risk of bias graph according to Cochrane Handbook for Systematic Review Intervention (Higgins, & Green, 2017).

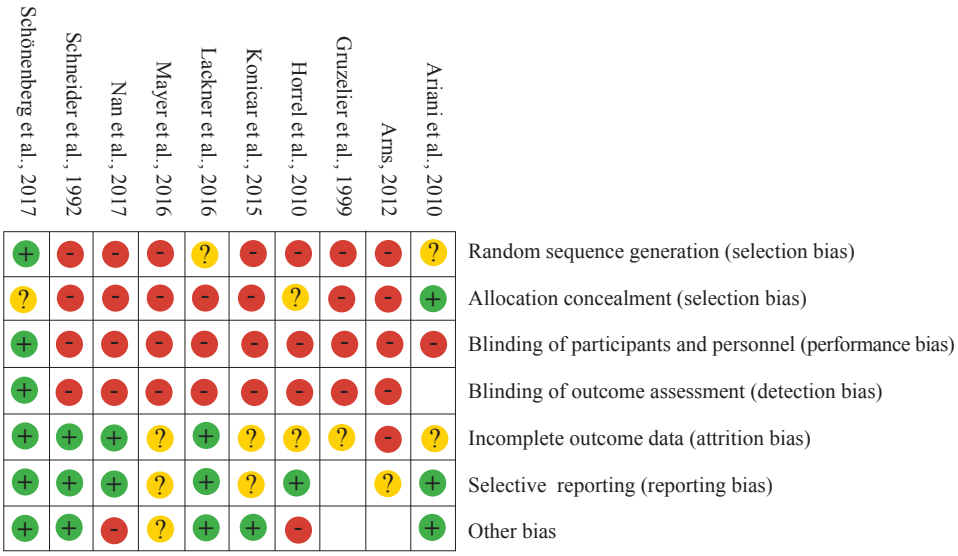


Figure 3. Risk of bias table according to Cochrane Handbook for Systematic Review Intervention (Higgins, & Green, 2017).

Table 1. Characteristics of the included studies (N=10)

Author(s) Year N (sex) Medicated (Yes/No)	**Protocol, electrode position, number of sessions**	**Control group (Yes/No) Moment of measurement**	**Change in EEG-parameters investigated by**	**Behavioral change investigated by**	**Criterion established for EEG-learning (Yes/ No)**	**Results (1) Symptom change** ↑Improvements ($p < .05$) <> = no change, **(2) Change in EEG-frequencies** ↑ Sign. increase in mean frequency ↓ Sign. decrease in mean frequency <>no change **(3) Results concerning for EEG-learning**
ADHD/ADD						
Arns et al., 2012 N= 21 ♂/ ♀ Yes (some patients)	QEEG Informed protocols: Beta↑/ Theta↓/Alpha↓; or Beta↓; or SMR↑/ Theta↓ (+ possibly alpha ↑); or SMR↑; individual electrode position; mean number of sessions 33.62	No Pre-training, Mid-training and Post-training	Changes in power in IAF, SMR, beta frequency bands and ERP measures	MINI PLUS/MINI PLUS KID, BDI (Inattention, hyperactivity/ impulsivity, depression scores)	No	(1) Inattention↑, hyperactivity / impulsivity↑, depressive symptoms↑ Response rate was 76% (16 out of 21) on behavioral measures. (2) SMR power↓, alpha, beta <> *[1]
Mayer et al., 2016 (Mayer et 2012)*2 N= 24, ♂/ ♀ Yes	SCP ↓↑; Cz; 30 sessions	No Pre-, Mid-, Post-training and six months follow-up	Changes in CNV mean amplitude with Go/No Go ERP task	ADHD-SB, WRI, FEA, FERT,	Yes: learners/ non-learners based on ability to differentiate between negativation/ positivation in transfer condition of last 3 sessions.	(1) Self-rated ADHD symptoms↑, third-party rated ADHD symptoms↑, depressive symptoms↑, state & trait anxiety↑ Reaction time & reaction time variability↑ (2) CNV showed a trend of increase over time. (3) 13 learners vs 11 non-learners. Trend towards larger improvements of self-rated ADHD symptoms in learners. Higher improvements of self-rated symptoms for learners at follow-up *[2]

Schönenberg et al., 2017 N = 113 ♂/ ♀ Yes	Theta (4-8 Hz)↓; Beta (13-21 Hz)↑; 30 sessions	Yes: Sham-NFB/Meta-cognitive group therapy (MCT) Pre-training, Mid-training, Post-training and follow-up	Changes in mean theta/beta ratio	CAARS, BDI-II, STAI-state, FPTM-23, TAP, Stroop, CPT, INKA	No	(1) Inattention↑, hyperactivity↑, impulsivity↑, anxiety symptoms↑, depression↑, TAP flexibility↑, reaction time <>, No superiority of NFB as compared to control groups (2) Theta/Beta ratio <> *[3]
Substance Use Disorder						
Arani et al., 2010 N= 20 ♂ Yes	Alpha (8-11 Hz)↓/ theta (5-8 Hz)↑, after crossover alpha + theta↑ while delta (2-5 Hz)↓ at Pz; SMR (12-15 Hz)↑ at Cz; 30 sessions	Yes: control group, no NFB Pre- and Post-training	Changes in power of delta, theta, alpha, SMR and high beta	SCL-90, HCQ	No	(1) SCL-90: Somatization, Obsession, Interpersonal Sensitivity, Psychosis, Hostility, total score↑*[4] HCQ: Anticipation for positive outcome, desire to use, relief from withdrawal↑ Intention and plan to use <> (2) Delta↓ (central and frontal), theta↓, (central area), alpha↓ (parietal and frontal areas), SMR↑ (frontal, central area)
Horrell et al., 2010 N= 10 ♂/ ♀ No	SMR (12-15 Hz)↑ at C3/Theta (4-7 Hz)↓ at F3; 12 sessions	No Pre- and Post-training	Changes in mean amplitude of theta, SMR frequency and ERP measures	BDI-II (PTSS and depressions scores), PSS-R, cue-reactivity test, drug testing	No	(1) Cue-reactivity test: Reaction time <>, accuracy <> Depression / Stress↑ Drug testing; positive drug testing↑*[5] (2) SMR↑ (mean increase 17%), theta <> Cue reactivity test: Gamma responses to drug cues↓

Lackner et al., 2016 N= 25 ♂ Yes	Alpha (8-12 Hz) ↑ at Pz; Theta (4-7 Hz)↑ at Fz; 12 sessions	Yes: TAU Pre- and Post-training and 6 months-follow-up	Changes in absolute and relative band power for theta, alpha and beta frequency band	ACQ-R, BDI-V, BSI, FKV-lis, FPTM-23, PPR, SOC, perceived control over EEG, belief in efficacy of training	No	(1) No significant results for behavioral outcome measures post-treatment Perceived control of EEG↑, belief in efficacy of training↑ (2) Trend towards higher alpha, theta power↑, beta <> *[6] No significant effects found at follow-up.
Schizophrenia						
Gruzelier et al., 1999 N= 25 ♂/ ♀ Yes	SCP ↑↓; C3/C4; 10 sessions	No Improvements within and between sessions	Changes in self-regulation of interhemispheric negativity over course of training		Yes: Good vs average performers based on visual inspection of NFB-sessions, first 5 sessions vs last 5 sessions	(2) Ability of patients to learn self-regulation of interhemispheric negativity. (3) Good performers had lateral shifts about twice as large as average performers ($p < .058$). *[7]
Nan et al., 2017 N= 1 ♀ Yes	IAF↑ Beta 2 (20-30 Hz)↓ 12.5 hours in 4 days	No Pre- and Post-training	Mean relative amplitude in individual theta, alpha, sigma band, beta 1 (16-20Hz)	Short-term memory test		(1) Memory↑ (2) Trend to increased IAB amplitude, trend towards decrease in relative beta 2 amplitude. *[8]
Schneider et al., 1992 N= 24 ♂ Yes (patients only)	SCP ↑↓; Cz; 20 sessions for patients, 5 for healthy controls	Yes: Two groups, both receiving NFB: 1. schizo-phrenic patients 2. Healthy controls Pre- and Post-training	Changes in mean differentiation of SCP over course of training		Yes: Learning success defined as mean difference between required negativity increase and negative suppression	(3) Patients were less efficient in SCP self-regulation than controls, patients were only able achieve differentiation of feedback trials comparable to controls in the last three sessions of training. *[9]

Psychopathy						
Konicar et al., 2015 N=14 ♂	SCP↑↓; Fcz; 25 sessions	No Pre- and Post-training	Changes in mean differentiation of SCP for first 6 sessions vs last six sessions	FAF, BPAQ, BIS/ BAS, Flanker Test	Learning investigated, but no criteria as to group patients	(1) Physical aggression↑, behavioral approach↑ Reaction time↑, commission errors↑ (2) Increase in SCP differentiation, but not for transfer conditions (3) Learning progress over the whole 25 training sessions showed a significant increase of SCP differentiation for the feedback condition as well as for the transfer condition over time.*[10]

*[1] *No effect sizes given.*
*[2] *The article by Mayer et al. (2016) and Mayer et al. (2012) refer to the same study. Description is based on Mayer et al. (2016).* *[2.1] *Cohens'd effect size d= 1.09*
*[3] *Effect size within-participant 1:00 for NFB, 1 : 51 for sham, and 1: 41 for mct*
*[4] *Effect sizes for significant results on the SCL-90 ranged from .4 to .75. Effect sizes for HCQ ranged from = .32 to .45.*
*[5] *No effect sizes given*
*[6] *For absolute alpha .139, theta .111*
*[7] *No effect sizes given*
*[8] *No effect sizes given, forward digit test improved from 7 to 9, backward digit test improved from 5 to 6.*
*[9] *No effect sizes given*
*[10] *No effect sizes given*

Abbreviations:
Number of participants (N) based on initial inclusion.
IAF= individual alpha frequency; MINI/MINI KID= structured ADHD interview; BDI-(II to V)= German version of Beck Depression Interview; ADHD-SB = Current ADHD questionnaire as part of HASE; WRI= ADHD Wender- Reimherr Interview; FEA= ADHD symptom questionnaire; FERT= questionnaire to assess expectancy with regard to treatment; CAARS= Conners' Adult Rating Scale; STAI= Anxiety questionnaire; FPTM-23= Therapy Motivation Questionnaire; CPT = continuous performance test; INKA= inventory for complex attention; SCL-90= Symptom Checklist-90; HCQ-45= Heroin Craving Questionnaire; PSS-R= Posttraumatic Symptom Scale – Self Report; ACQ-R= Alcohol Craving Questionnaire Revised Form; BSI= Brief Symptom Inventory; PPR= Posttraumatic Growth Inventory; SOC= Sense of Coherence Scale; FAF= Assessment of aggressiveness factors; BPAQ= Buss-Perry-Aggression Questionnaire; BIS/BAS= Behavior-Inhibition/Behavior-Activation System Questionnaire.

Discussion

This study set out to review studies that applied neurofeedback in criminal offending and the disorders these patients usually present with. Only studies that described whether or not neurofeedback led to changes in trained EEG treatment parameters were considered. To the best of our knowledge, this is the first review that investigates neurofeedback training for the purpose of applying it in the treatment of criminal offenders. The review identified 10 studies, of which three studies concentrated on neurofeedback training in patients with ADHD, three on patients with substance use disorder, three on schizophrenia, and one on offenders with psychopathic traits. No studies fitting the inclusion criteria could be identified for neurofeedback applied in patients with cluster B personality disorders, or for reducing violence or recidivism in criminal offenders. For all treatment populations and applied neurofeedback protocols taken into account, the number of neurofeedback sessions varied greatly, ranging anywhere from 10 to 30 sessions. Most sessions were applied in patients with ADHD (about 30 sessions), whereas number of sessions was smaller in patients with schizophrenia (10-20 sessions). Possibly, patients with ADHD are more able to undergo a large number of treatment sessions than patients with schizophrenia, which are more disabled when it comes to adhering treatment due to their negative symptoms (Lyne, et al., 2016). In the study by Nan et al. (2017), an intense four day neurofeedback training protocol was applied. Unfortunately, level of negative symptoms was not assessed and no indication about patient motivation for treatment was given, so it remains unclear whether individual characteristics of the patient (such as the high degree of education) contributed to the patients ability to follow such an intense training protocol.

With regard to the behavioral results of the studies in this review, neurofeedback research for criminal offenders might benefit most from studies where improvements were found for levels of impulsivity (Arns et al., 2012; Mayer et al., 2016; Schönenberg et al., 2017), psychopathy (Konicar et al., 2015), hostility (Arani et al., 2010), and drug use (Arani et al., 2010; Horrell et al., 2010), which are all very often present among forensic psychiatric patients. Impulsiveness is a strong predictor of criminal offending, and the difficulties with inhibitory control make these patients more prone to aggressive outbursts and violent behavior (e.g., Reddy et al., 2014; Swann, Bjork, Moeller, & Dougherty, 2002). Substance use is associated with higher rates of violence (Dugré, Dellazizzo, Giguère, Potvin, & Dumais, 2017). Reducing these symptoms by neurofeedback might be promising with regard to the reduction of recidivism. The results of these studies are mixed with regard to post-treatment changes in the targeted EEG-frequency bands, with results ranging from no significant changes, trends towards significance, to significant changes in the desired direction.

A central hypothesis in neurofeedback research is that the positive effects of the training are due to a feedback-driven training of specifically targeted frequency bands (Schönenberg et al., 2017). However, even in studies where EEG-frequencies did not significantly change post-treatment (Schönenberg et al., 2017), or even changed in the opposite direction as intended with the training protocol (Arns et al., 2012), clinical improvements could still be observed. Also, in the study by Lackner et al. (2016), no behavioral improvements could be observed, while changes in theta and alpha power were significant by trend post-treatment (however, patients' belief in the efficacy of training and the perceived control of EEG-activity increased over the course of training). It is to be expected that a patients' ability to learn principles of neurofeedback should be correlated

with changes in clinical symptoms. In the study by Konicar et al. (2015), level of participants' SCP-differentiation was positively correlated with improvements on behavioral measures. In Mayer et al. (2016), a trend towards higher improvements of ADHD symptoms for EEG-learners could be observed. In the study by Schneider et al. (1992), EEG-learning success correlated negatively with symptomatology at the beginning of the study, history of illness, and number of hospitalizations, so possibly, neurofeedback is easier for patients with less severe courses of illness. Based on the studies in this review, no final conclusion can be drawn about whether positive effects of neurofeedback are due to specific neurophysiological changes.

There is still an ongoing debate about whether improvements in clinical symptoms post-neurofeedback training are due to other, non-specific effects, such as perceived self-efficacy (Barth, Mayer, Strehl, Fallgatter, & Ehlis, 2017), therapist-patient interaction and/or increased ability to focus on the neurofeedback training at hand. Only four studies in this review compared the effects of neurofeedback to a control group (Arani et al., 2010; Lackner et al., 2106; Schneider et al., 1992; Schönenberg et al., 2017). While some of the unblinded trials in this review revealed improvements in clinical symptoms after neurofeedback training, the triple-blind, randomized controlled trial by Schönenberg et al. (2017) showed no superiority of neurofeedback training over sham-neurofeedback and meta-cognitive group therapy. Most of the studies included in our review also had a high risk of bias, which was mostly due to the lack of a control group and blinding of participants and therapists. The use of adequate control groups is an ongoing debate in the literature. Sham-neurofeedback training often times contains of training seemingly irrelevant frequency bands that are typically in the higher beta or gamma bands. However, some studies show that alterations in EEG-frequency bands post-treatment can still be observed, even though these frequency bands were not up- or down-trained during the intervention (e.g., Doehnert et al., 2008). It is therefore possible that effects found in sham-neurofeedback conditions are due to training of seemingly irrelevant frequency bands. The use of an EMG-biofeedback as an adequate control group is also highly questionable, as a recent study by Barth et al. (2017) showed that even EMG-biofeedback resulted in an increase of alpha power post-treatment. It is clear that more research on adequate control groups is needed.

For forensic psychiatric patients with multiple comorbidities, QEEG-deviations might not match with the frequency bands that are up- or down-trained in standard neurofeedback protocols. In this review, most studies only investigated differences between groups pre-treatment, but did not investigate whether QEEG deviations at baseline actually matched the employed neurofeedback protocol. Clarke et al. (2011) for example, identified three different EEG-frequency clusters in children with ADHD, who also presented with significantly different behavioral complaints between groups. They identified a subgroup who presented with increased delinquent behavior, but who showed an increased beta activity and a decreased theta activity instead of the cortical underarousal often used as an indicator for lack of inhibitory control. More research is still needed about how these EEG-deviations manifest in ADHD adults, but it can be argued that these patients will most likely not profit from a standard theta/beta neurofeedback protocol.

The success of neurofeedback training for complex combinations of disorders might also be found in secondary factors such as treatment retention and teaching patients to cope with stress, rather than successfully normalizing (all) QEEG-deviations. Individuals with high levels of impulsivity (such as often seen in ADHD and/or SUD) more often fail to complete treatment programs (Moeller et al., 2001; Wilens, 2004), which in turn increases risk for recidivism.

In a study by Scott et al. (2005), the Scott-Kaiser modification of the Peniston Protocol was employed in subjects presenting with SUD and attention-deficits, and while the study does not report outcomes on a neurophysiological level, participants remained in treatment significantly longer than controls. For criminal offenders, risk for criminal recidivism will almost certainly benefit from keeping patients in treatment. Furthermore, studies have shown that neurofeedback (especially alpha-theta protocols) can be effective in improving mentalization (Imperatori et al., 2017). Poor mentalization skills are believed to at least partially underlie aggressive behavior in antisocial personality disorder (Velotti et al., 2016). Improving mentalization skills could serve as a protective factor toward preventing aggression among criminal offender populations (Velotti et al., 2016).

None of the studies investigated in this review report serious side effects of neurofeedback training. With medication for disorder such as ADHD and schizophrenia, side effects tend to be quite stressing and uncomfortable for patients. Also, positive effects of medication tend to diminish once medication use is terminated. Often times, the efficacy of neurofeedback is questioned as it has not been shown to be superior to medication. Yet, some studies do show comparable effects of medication and neurofeedback (e.g., Fuchs et al., 2003; Janssen et al., 2017). If similar results can be achieved with neurofeedback as with medication, neurofeedback could be seen as the less invasive treatment with less possible side effects. This would especially be the case when applied in vulnerable patients populations.

Conclusion

More research focusing on neurofeedback and actual learning of cortical activity regulation is needed in populations with externalizing behaviors associated with violence, criminal behavior, and oftentimes multiple comorbidities. Although large randomized controlled trials are considered the gold standard in scientific research, it is questionable whether studies with criminal offenders can adhere to these strict standards, due to low levels of treatment compliance of criminal offenders making it difficult to engage these patients in scientific research (Van Outsem, 2011). Clinical trials, as well as single-case experimental designs (e.g., Fielenbach, Donkers, Spreen, & Bogaerts, 2017), where some compromises in research methodology and experimental controls have to be made, but where treatment is tailored to the individual and his/her clinical complaints (Rossiter, & LaVaque, 1995) might be more feasible than large double-blind randomized controls. The study by Nan et al. (2017) explored the effects of neurofeedback training in a single subject design, but unfortunately, improvement in clinical symptoms was not investigated systematically. However, the methods used in clinical trials can provide the same level of experimental rigor and internal validity (Rizvi, & Nock, 2008) if executed correctly, and might help shed light on applicability of neurofeedback in criminal offenders and possibly help reduce risk of recidivism.

Chapter 3

Neurofeedback as a treatment for impulsivity in a forensic psychiatric population with substance use disorder: study protocol of a randomized controlled trial combined with an n-of-1 clinical trial

Published as: Fielenbach, S., Donkers, F. C. L., Spreen, M., & Bogaerts, S. (2017). Neurofeedback as a Treatment for Impulsivity in a Forensic Psychiatric Population With Substance Use Disorder: Study Protocol of a Randomized Controlled Trial Combined With an N-of-1 Clinical Trial. JMIR Research Protocols, Jan 25;6(1):e13. doi:10.2196/resprot.6907

Abstract

Impulsivity and substance use disorder (SUD) are strongly interconnected, with persons scoring high on impulsivity being more vulnerable to develop substance abuse, facing more challenges for successful treatment, and being more prone to engage in criminal behavior. Studies have shown that impulsivity and craving for substances are strongly correlated. Neurofeedback is an effective treatment to reduce impulsive behavior. This study intends to determine to what extent a neurofeedback intervention that is aimed at reducing impulsivity can also reduce levels of craving in forensic patients with SUD and comorbid Axis I and/or II diagnoses. The main objective of this study is to investigate to what extent a reduction in impulsivity by a sensorimotor rhythm (SMR) neurofeedback intervention will lead to a reduction in craving in a population of forensic psychiatric patients with a diagnosis of SUD. Participants will be male SUD patients with various comorbidities residing in an inpatient forensic treatment facility approached through treatment supervisors for participation. Participants have tested positive for drug use in the past 24 months. The study consists of 2 parts: a randomized controlled trial (RCT) and a n-of-1 clinical series. In the RCT, 50 patients will be randomly assigned to an intervention (n=25) or a control (n=25) condition. Patients in the intervention group will receive 20 SMR neurofeedback sessions aimed at reducing impulsivity; participants in the control group receive treatment as usual (TAU). Additionally, 4 in depth n-of-1 clinical trials will be conducted where effects of an SMR neurofeedback intervention will be compared to effects of sham neurofeedback.
Results of this study are expected by the end of 2017. This protocol describes the design of a study testing the effects of an impulsivity-based neurofeedback protocol among forensic patients with SUD and various comorbidities. We expect a significant reduction in impulsive behavior, level of craving, and actual drug-use for participants receiving the SMR neurofeedback protocol. The n-of-1 approach might help to explain effects possibly found in the RCT study since it allows for a more direct focus on treatment effects by following participants more closely and thereby being able to directly attribute behavioral and neurophysiological change to the SMR neurofeedback protocol employed.

Background

Impulsivity has been defined as a dysfunctional trait, leading to a tendency for an individual to display behavior that is performed with little or inadequate forethought (Evenden, 1999) and might be criminal and possibly harmful to oneself or to others (Verdejo-Garcia, Lawrence, & Clark, 2008). Impulsivity has been operationalized in different ways with inadequate behavioral inhibition being conceived as one of the key factors (Loree, Lundahl, Ledgerwood, 2015). Impulsive behavior is hypothesized to involve a disinhibition of cognitive control that occurs without conscious deliberation (Nielsen et al., 2012).

Several studies have demonstrated that substance use disorder (SUD) is strongly associated with elevated impulsivity scores on various measures (Loree et al., 2015). In SUD, the use of a substance is continued even though a person is aware of the negative consequences of prolonged drug use. This can be explained by deficient inhibitory control over drug-taking which provides immediate (positive) reinforcement (Verdejo-Garcia et al., 2008). Higher levels of impulsivity were found in individuals scoring high on alcohol, stimulant, and opiate use (Loree et al., 2015), as measured by self-report instruments, such as the Barratt Impulsivity Scale (BIS-11) (Nielsen et al., 2012). Individuals with combined cocaine and alcohol abuse show impaired response inhibition as compared to controls on continuous performance tasks measuring impulse control such as the Cued Go/No-Go task (Fillmore & Rush, 2006). Furthermore, a strong relation between elevated impulsivity scores during childhood/early adulthood and substance abuse problems later in life has been observed, indicating that heightened levels of impulsivity might precede the development of substance abuse problems (in Hawkins, Catalano, & Miller, 1992, for example). In alcoholism for example, behavioral disinhibition as assessed with a novelty-seeking scale has been shown to predict early onset alcoholism (Howard, Kivlahan, & Walker, 1997). Individuals scoring high on impulsivity are therefore more prone to develop SUD than healthy controls and more often exhibit antisocial behavior (Howard et al., 1997).

The concept of impulsivity has been of particular interest in studies involving criminal offenders, as these individuals often suffer from major mental disorders and are therefore more likely to be involved in criminal acts than persons without major mental disorders (Kamperman et al., 2014). In criminal offenders, cluster B personality disorders and schizophrenia are frequently diagnosed (Van Nieuwenhuizen, Bogaerts, Ruijter, Bonges, & Coppens, 2011). Comorbidity rates between these disorders and SUD are as high as 70% (Van Nieuwenhuizen et al., 2011). Generally, treatment of SUD has proven to be difficult, with relapse rates as high as 60% after treatment in opiate abusers (Marissen, Franken, Blanken, Van den Brink, & Hendriks, 2005). For patients with a criminal history and a combination of SUD and comorbid disorders characterized by high levels of impulsivity, long-term treatment outcomes are worse (Van Nieuwenhuizen et al., 2011). High impulsivity levels predict both early relapse and increase chances of premature termination of treatment (Charney, Zikos, & Gill, 2010). This, in turn, increases the risk of recidivism in criminal behavior (Trimbos, 2008). Adequate treatment for this vulnerable patient population is therefore extremely important, as impulsivity can be understood as an important risk factor in both the onset of SUD as well as post-treatment relapse (Bozkurt et al., 2014).

Neurofeedback Treatment for Impulsivity and Substance Use Disorder

Electroencephalographic (EEG) spectral analysis is a frequently used method to compare healthy

controls with prolonged drug users by focusing on differences in the (relative) strength of naturally occurring rhythms in the EEG (in Alper, Prichep, Kowalik, Rosenthal, & John, 1998), for example). EEG alterations most commonly found in individuals with SUD are characterized mainly by alterations in the strength of theta (4-8 Hz), alpha (8-12 Hz), and beta (12-20 Hz) frequency bands (Dehghani-Arani, Rostami, & Nadali, 2013) and are hypothesized to be related to symptoms of drug use disorder, such as over attention to drug cues, feelings of restlessness, and loss of impulse control. Although alterations in several EEG spectral measures have been observed that vary by type of addiction, they persist even after drug abuse is in remission (Alper et al., 1998).

Neurofeedback is an intervention that uses real-time EEG measurements and displays information about these EEG measurements back to the participant, allowing them to not only see but also change their brain electrical activity over time (Sokhadze, Stewart, Tasman, Daniels, & Trudeau, 2011). By principles of operant conditioning, participants learn to reinforce or inhibit specific frequencies of the EEG activity (Scott, Kaiser, Othmer, & Sideroff, 2005) and thereby normalize abnormal EEG states, which in turn aims at changing abnormal psychological states (Gunckelman & Johnstone, 2005). Sensors are placed on the scalp and moment-to-moment information about brain activity is fed back to the participant (Hammond et al., 2011).

Several studies have shown neurofeedback to be a promising intervention for various disorders, ranging from SUD to attention deficit hyperactivity disorder (ADHD) (Sokhadze et al., 2011). In SUD, a widely used neurofeedback protocol is the Scott-Kaiser modification of the Peniston Protocol, consisting of a combination of sensorimotor rhythm feedback (SMR, 12-15 Hz) followed by alpha-theta based feedback (Scott et al., 2005). With this type of protocol, patients first receive neurofeedback that focuses on reinforcing SMR (12-15 Hz) while inhibiting slower frequencies such as delta (2-5 Hz) and theta (5-8 Hz) and also inhibiting high beta (ranging from 18-30 Hz) (Dehghani-Arani et al., 2013; Scott et al., 2005). This type of feedback is first employed for 10 to 20 sessions before the neurofeedback protocol is switched to an alpha-theta based protocol, where alpha (ranging from 8-12 Hz) is decreased while theta (5-8 Hz) is augmented until the amplitude of alpha drops below the level of theta (Dehghani-Arani et al., 2013; Scott et al., 2005). The Scott-Kaiser modification of the Peniston Protocol has shown to be effective in opiate dependent patients as well as in patients with a mixed substance dependency, as it led to the reduction of feelings of craving (Scott et al., 2005), a powerful predictor of relapse in drug-taking (Paliwal, Hyman, & Sinha, 2008; Weiss et al., 2003), and therefore promoted treatment attendance and abstinence rates of participants (Scott et al., 2005). As most criminal offenders with SUD also suffer from comorbid psychiatric conditions however, treatment with neurofeedback may become more complicated (Sokhadze et al., 2011). For patients having a combination of impulsivity issues due to comorbidity with other psychiatric disorders, as well as substance abuse problems, it is suggested that a SMR-enhancing neurofeedback protocol should be applied to address the issue of impulsivity first (Trudeau, 2005). Studies performing a neurofeedback protocol consisting of suppressing slow waves such as theta (4-7 Hz) and enhancing faster waves such as SMR (12-15 Hz) have demonstrated an improvement of impulse control in a population of students (in Egner & Gruzelier 2004, for example) and have shown to positively affect motor control and cortical inhibitory function (in Sokhadze et al., 2011, for example). This type of neurofeedback protocol is also commonly applied with patients suffering from the hyperactive-impulsive ADHD subtype and there are many studies reporting reduction in impulsivity after treatment

(in Fuchs, Birbaumer, Lutzenberger, Gruzelier, & Kaiser, 2003). Several studies have shown that impulsivity and craving for substances are strongly correlated no matter the administered drug of choice. For example, in a study by Tziotzis, Mahoney, Kalechstein, Newton, and De la Garza (2011) with methamphetamine users, individuals with higher levels of impulsivity reported significantly more craving than individuals scoring lower on impulsivity. In alcohol dependent patients, higher scores of craving were correlated with higher self-reported impulsivity on the BIS-11 (Joos et al., 2013). Moeller et al. (2001) found a significant correlation between the motor impulsivity subscale of the BIS-11 and craving in a population of cocaine dependent subjects. Also for cocaine dependent patients, higher impulsivity was associated with greater severity of addiction symptoms such as craving (Bornovalova, Levy, Gratz, & Lejuez, 2010; Ledgerwood & Petry, 2010). Also, contemporary neuropsychological models stress impulsivity and SUD to be the result of the same imbalance between bottom-up and top-down neural systems (Bechara, 2005; Heatherton & Wagner, 2011). Bottom-up systems concern subcortical brain circuitry promoting impulsive reward behavior (regardless of long-term outcomes), whereas top-down processes concern reflective and self-control functions driven by prefrontal brain circuitry (Stevens et al., 2014). Within SUD, chronic substance abuse may produce neural changes leading to a structural state of disinhibition and impulsivity (Bates, Bowden, & Barry, 2002; Jentsch & Taylor, 1999), causing immediate reaction to substance-related cues that elicit craving (Lyvers, 2000). Not only acute but also prolonged effects of substance abuse have proven to be of great influence in disrupting these neuropsychological mechanisms, therefore maintaining problems with inhibitory control even after drug use is terminated (Roozen, van der Kroft, van Marle, & Franken, 2011). Although impulsivity and craving are both independently identified as key elements in SUD, to date, there has been no study investigating whether a reduction in one will also lead to a reduction of the other.

This Study

Although the relationship between impulsivity and symptoms of SUD such as craving and actual drug use has been established, to date there is no evidence about the effects of an impulsivity based neurofeedback protocol and its effectiveness on impulsivity and on symptoms of SUD. This study aims to examine the treatability of impulsivity with an SMR neurofeedback intervention in a population of forensic psychiatric patients with SUD and comorbid Axis I and/or II disorders. It also aims to investigate whether a reduction of impulsivity through an SMR-based neurofeedback protocol will also result in a reduction of SUD symptoms such as craving and actual drug use.

The study will combine a randomized controlled trial (RCT) design with an n-of-1 clinical trial. The RCT allows for investigating to what extent a SMR neurofeedback protocol can reduce craving and actual drug use by augmenting levels of impulsivity for forensic psychiatric patients at a group level. However, RCTs have several disadvantages. First, they focus on between-group differences, making it difficult to determine the exact working mechanisms of neurofeedback at the single patient level. Despite the fact that the number of studies employing neurofeedback has increased over the past 2 decades, to date the underlying working mechanisms of neurofeedback remain unclear. Success of treatment is usually determined by a reduction in subjective complaints or based on other behavioral measures, independent of patients' responses to neurofeedback on a neurophysiological level (e.g., change in mean amplitude of brain frequencies). Second, most RCTs focus on participants with single, well-defined disorders or diagnoses, making it difficult

to apply previous findings to patients who have a more complex psychopathology as is usually the case in forensic patients. Third, finding a reduction in subjective complaints could partially be explained by the interaction with the person giving the treatment, as this occurs with almost all frequently given types of therapy in the psychological field (Horvath & Symonds, 1991). To rule this out, large RCTs with a treatment and a sham arm are necessary. Unfortunately, these studies are very difficult to conduct in a forensic psychiatric setting due to the fact that forensic patients generally have low levels of treatment compliance (van Outsem, 2011). As the current study concerns a single-site study with only a limited number of patients who fit the inclusion criteria to begin with (but on forehand sufficient according to power analysis), adding a sham arm to the RCT would most likely further reduce the motivation of patients to participate and hence increase nonresponse. However, insight in possible sham effects is needed to differentiate between specific and nonspecific treatment effects which are independent of the neurofeedback trainer. Finally, RCT studies showing treatment effects of neurofeedback often vary in the applied protocols, number of sessions, and treatment intensity. To date, there have been no guidelines developed that specify these neurofeedback parameters. Especially for forensic patients, developing a treatment that is well applicable and helps to reduce symptoms of SUD is of great importance, as forensic treatment is aimed at protecting society and reducing the risk of reoffending. By adding several n-of-1 clinical trials we attempt to cope with these disadvantages. A well conducted n-of-1 trial allows testing of the specific working mechanisms of neurofeedback in a single patient and is therefore able to detect detailed behavioral and neurophysiological changes that can then be attributed more definitely to neurofeedback treatment.

Objectives

Primary outcome variables are the degree of impulsivity as measured with the Dutch version of the Barratt Impulsivity Scale (BIS-11) (Lijffijt & Baratt, 2005); inhibitory control as measured with a cued Go/No-Go reaction time task (Fillmore, 2003); degree of drug craving as measured with an altered version of the Desire for Alcohol Questionnaire (DAQ) (Franken, Rosso, & Van Honk, 2003); actual drug use as measured with urine, saliva, or breathalyzer analysis; and changes in resting state EEG pattern.

Primary objective: To what extent does a reduction in impulsivity by using SMR neurofeedback result in a reduction of core symptoms of SUD such as craving and actual drug use in a population of forensic psychiatric patients with a diagnosis of SUD?

Secondary objectives:

1. To what extent can a SMR-based neurofeedback intervention reduce levels of impulsivity as measured by BIS-11 and a cued Go/No-Go task in a population of forensic psychiatric patients with a diagnosis of SUD?
2. To what extent can a SMR-based neurofeedback intervention reduce levels of craving as measured by self-report questionnaire DAQ-SF (short form) in a population of forensic psychiatric patients with a diagnosis of SUD?
3. To what extent can a SMR-based neurofeedback intervention reduce actual drug use as measured with urine, saliva, or breathalyzer analysis in a population of forensic psychiatric patients diagnosed with SUD?

Method

Overview

This study will be conducted according to the principles of the Declaration of Helsinki (version 59, Seoul, October 2008) and in accordance with the Medical Research Involving Human Subjects Act. It has been approved by the medical ethical council of Brabant, the Netherlands (study number NL46390.008.13).

This study takes place in Forensic Psychiatric Centre (FPC) Dr S van Mesdag, a maximum security inpatient forensic treatment facility in Groningen, the Netherlands. Patients in this treatment facility are male criminal offenders with at least one Axis I or II diagnosis and considered to be at risk for criminal recidivism if not treated properly. About 70% of all patients treated in this facility have a comorbid diagnosis of SUD. About 70% of all patients treated in this facility have a comorbid diagnosis of SUD (Van Nieuwenhuizen et al., 2011).

Randomized Controlled Trial

A randomized controlled trial with N=50, where 25 participants are randomly assigned to treatment as usual (TAU) combined with 20 SMR-based neurofeedback sessions and 25 participants are randomly assigned to TAU only, without neurofeedback intervention. The 2 groups are compared pretreatment (T0) and posttreatment (T1) on variables linked to the research questions. Both groups will receive pre- and post-treatment measurements with an interval between T0 and T1 of approximately 10 weeks in which participants in the intervention group will receive 20 neurofeedback treatment sessions and participants in the control condition will follow TAU.

The design of this part of the study is a 2×2 design with the condition (neurofeedback vs TAU) as a between-subjects factor and time as a within-subjects factor (pre- and post-intervention).

N-of-1 Clinical Trial

To zoom in on specific treatment effects, 4 single case studies with an $A^1B^1A^2B^2$ design (single time series) will be conducted, of which 2 single case studies will apply an actual SMR neurofeedback protocol and 2 single case studies will apply a sham neurofeedback training. The clinical trial will be single-blinded, indicating that participants do not know which part of the training they will receive. Participants are selected from the control group of the previously described RCT protocol who have already completed pre- (T0) and post-treatment (T1) measurements. Inclusion in the n-of-1 trial will be selective: participants with the highest scores on outcome measures on T1 of the RCT will be approached first as it is believed that these patients have the highest need for treatment. However, allocation to treatment (sham or real) will be random.

For a detailed description of this design of n-of-1 studies, see Rizvi and Nock (2008). Basically, in this design, a baseline period (A^1: no-treatment, lasting 3 weeks) is followed by a treatment period (B^1: neurofeedback, sham or real, lasting 4 weeks and resulting in 8 neurofeedback sessions), which is followed by a period where treatment is withdrawn (A^2: lasting 3 weeks). During all periods, outcome measures DAQ-SF and BIS-11 will be assessed 2 times a week. At the end of the A^2 period, statistical analyses are applied to test for significant improvements in study end points. In cases of significant improvement during treatment, a second period of neurofeedback, B^2 (sham or real), will be applied. This way, if neurofeedback does not prove to be effective within B^1, participants will not be burdened with the requirement of completing more sessions. It

is expected that patients who have not shown any significant improvement during neurofeedback sessions in B^1 will not show any further improvements when undergoing more sessions. After completion of the study, patients and treatment supervisors will be debriefed about whether the neurofeedback intervention was real or sham.

To test for transient effects of the neurofeedback intervention, a follow-up measurement of resting state EEG, BIS-11, DAQ-SF, and Cued Go/No-Go task will be performed 12 months after completing the post-treatment measures for both participants in the intervention group of the RCT and for participants in the n-of-1 clinical trial.

Participants

A power analysis calculation for the RCT using G*Power 3 (Faul, Erdfelder, Lang, & Buchner, 2007) based on a 1-tailed alpha value of .05, a power value of 0.80, and an effect size (*f*) of 0.80 yielded a recommended sample size of 21 participants each in the control and intervention conditions. Given the special research population we aim to select 25 participants for each condition.

Participants are male patients diagnosed with SUD (substance dependency or substance abuse) according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Review (DSM-IV-TR, American Psychiatric Association, 2000) and currently staying at the treatment facility. Participants have tested positive for drug use in the past 24 months at time of inclusion. Drug use is operationalized as urine, saliva, or breathalyzer analysis testing positive for either marijuana and/or psychostimulant/opioid drugs and/or alcohol. Corresponding with treatment facility policy, nonprescribed medication that is used for recreational drug consumption such as inhaled methylphenidate will also be scored as positive drug testing, as will refusal to undergo drug testing.

Participants are allowed to continue using prescription medication (as prescribed by a psychiatrist or general physician of the treatment facility) but are required to inform researchers of any medication they are currently using or any change in medication during treatment with neurofeedback.

Recruitment

Recruitment will start with the selection of patients for the RCT part of the study. Participants are approached through treatment supervisors for participation. Treatment supervisors are informed about the general inclusion criteria for this study. Out of all participants that meet the requirements, a random sample of 50 will be drawn and randomly assigned to 1 of the 2 conditions (intervention and control). Prior to participation in the trial all participants are asked to provide written consent. If at this point a participant chooses to not participate in the trial, this will be coded as a nonresponse. Missing numbers of participants will be complemented by randomized allocation of other suitable participants that are willing to participate in order to guarantee the sample size. Once all patients for the RCT have been recruited, recruitment for the n-of-1 clinical trial will begin. All participants will receive a financial reward after completing pre- and post-treatment measurements.

Measures

Electroencephalography. Participants will undergo a 21-channel EEG measurement with Nexus-32 hardware and Biotrace+ software (Mind Media BV). The EEG will be collected

from 19 standard 10/20 positions (Herbert & Jasper, 1958) and the right and left mastoid with a sampling rate of 512 samples per second. The left mastoid will serve as the online reference. Flat type electrodes will be placed above and below the left eye and at the outer canthi of each eye to correct for vertical and horizontal eye movements. Participants will be seated comfortably while 5 minutes of eyes closed resting state EEG data is collected. EEG measures will be conducted at T0 and T1 as well as at 12 months follow-up for participants in the intervention group (T2).
For participants in the neurofeedback group, a 1-minute baseline recording over 3 conditions will be conducted before start of the first neurofeedback session and after the last session. EEG signal will be recorded from electrode position Cz against a right ear mastoid reference across the conditions (1) eyes open, (2) eyes closed, and (3) cognitive task (where participants are instructed to solve simple mathematical calculations). These measurements will be used to determine neurofeedback threshold values and to assess change in mean magnitude of frequency bands before and after neurofeedback training.

Barratt Impulsivity Scale–11. The Dutch version of the BIS-11 (eleventh edition) (Patton, Stanford, & Barratt, 1995) is a self-report questionnaire designed to measure the behavioral and personality construct of impulsivity across 3 second-order factors: attentional, motor, and nonplanning. It consists of 30 items scored on a 4-point scale ranging from rarely/never to almost always/always. The BIS-11 has been proven to be an internally consistent measure of impulsivity among inmate populations (Patton et al., 1995).

Cued Go/No-Go Task. The cued Go/No-Go task is a continuous performance test measuring impulse control by the ability to inhibit prepotent responses (Fillmore, 2003). Participants are instructed to respond to a green square by pressing a button as quickly as possible while not responding to a blue square. A go or no-go cue is given before the actual target appears, providing information about the likelihood of an actual go or no-go target (Fillmore, 2003). The likelihood of a correct target after a cue is manipulated with a 80/20 ratio, with 80% being a correct cue and 20% being an incorrect cue. Cues are presented with 4 fixed stimulus onset asynchronies (100, 200, 300, and 400 ms), giving participants time to prepare for responding. The cued Go/No-Go task has been proven to be a useful measurement of impulse control in substance abusing populations (Fillmore, 2003). It consists of 250 trials spread over 5 rounds with a 30-second break in between each round, taking approximately 20 minutes to complete. Outcome measurements are omission (the participant does not respond when he should respond) and commission errors (the participant responds when he should not respond) and reaction time.

Modified Desire for Alcohol Questionnaire. The DAQ-SF (Courtney et al., 2013) is a self-report questionnaire assessing the desire to use drugs at the moment of assessment. It is derived from the original desire for alcohol questionnaire (DAQ) with 36 items. The short-form version of the DAQ consists of 14 item that can be scored on a scale from 1 to 7 ranging from strongly disagree to strongly agree. It consists of 3 factors: (1) strong desires/intention to drink, (2) negative reinforcement, and (3) ability to control drinking. The abbreviated version has been shown to be reliable in measuring alcohol craving (Courtney et al., 2013).
All questions of the original questionnaire are designed to measure craving purely for alcohol; however, within the treatment facility alcohol use is less common than other drug use (such

as marijuana and/or cocaine). Therefore, questions from the questionnaire have been altered so they can fit any type of drug dependency. An example of this is "My desire to drink seems overpowering" which has been altered to "My desire to use drugs seems overpowering."

Instrument for Forensic Treatment Evaluation. The Instrument for Forensic Treatment Evaluation (IFTE) is an observational treatment evaluation instrument consisting of 22 items measuring 3 factors: Problematic behavior, protective behavior, and resocialization skills. It is scored on a 17-point Likert scale with 5 anchor points: none, rarely, sometimes, often, and always (Schuringa, Spreen, & Bogaerts, 2014). The IFTE assesses forensic risk behaviors such as impulsivity, hostility, and violating treatment conditions. These risk behaviors might be manifestations of impulsive behavior and could help assess engagement in impulsive behavior that is not assessed by the BIS-11 and the cued Go/No-Go task. Furthermore, the IFTE also assesses cooperation with treatment, which measures the amount of effort a patient puts in to make progress in his treatment, giving an indication of the degree of commitment (and thereby, motivation) of a patient to forensic treatment. The IFTE is scored twice a year by clinicians involved in patients' treatment as part of routine outcome measurement within the treatment facility. Patients also score the IFTE on a self-report version of the original IFTE (IFTE-SR), where they can give an indication of treatment progress during the past 6 months. Scores of the IFTE and IFTE-SR are assessed from the moment a patient arrives at the treatment facility up until release. Therefore, scores on the IFTE are available throughout the research. Relevant scores included in this study will be assessments 6 months prior to inclusion up until 12 months after the last measurement.

Actual Drug Use. Drug testing is performed on a regular basis, usually once every 2 weeks. Whenever staff suspects illegal use of substances within 2 moments of drug testing, spontaneous and unexpected drug testing can be performed. Number of drug tests will be counted, as will be positive (meaning drug use in the period of time since last drug test) and negative (meaning no drug use since last testing) outcome scores. Drug testing is done in the form of urine, saliva, or breathalyzer (for alcohol use only) analysis.

Covariates. Covariates are sociodemographic characteristics; specific psychopathology; duration of forensic treatment; actual drug use during the past 24 months (or as long as patients reside in the treatment facility); medication use; clinical risk assessment score (Historical/Clinical/Future-Revised, HKT-R) (Spreen, Brand, Ter Horst, & Bogaerts, 2014); actual drug use; and mean score of delta, theta, alpha, beta, and gamma resting state EEG-frequency band power. Covariates will be collected through case file information. Medication and medication change will be categorized according to class of medication (e.g., benzodiazepines, antipsychotic medication).

Intervention

All participants already receive TAU at the moment of inclusion. They will continue to do so during the course of this trial. Type of TAU is dependent on disorder and behavior but can range from cognitive behavioral therapy, psychotherapy, and psychomotor therapy to relapse prevention treatment and can be either individual treatment or in-group treatment. Treatment can also be supplemented by medication for psychotic symptoms or depressive symptoms, for example. In

some rare cases, aversion or craving reducing medication is prescribed.
Participants in the intervention condition of the RCT will receive 20 neurofeedback sessions, each lasting approximately 40 minutes. EEG magnitude is measured across delta (0.5-3.5 Hz), theta (3.5-7.5 Hz), alpha (7.5-12 Hz), beta (12-20 Hz), SMR (12-15 Hz), high beta (20-32 Hz), and gamma (32-49 Hz) frequency bands. To reduce inattention and impulsivity, a conventional neurofeedback protocol will be used that consists of suppressing theta magnitude and enhancing SMR magnitude (Lubar, Swartwood, Swartwood, & Timmermann, 1995; Linden, Habib, & Radojevic, 1996). The aims of the neurofeedback sessions are therefore to reduce slow waves (specifically theta, 3.5-7.5 Hz, and if necessary delta, 0.5-3.5 Hz) and increase faster waves (SMR, 12-15 Hz). A maximum of 3 different frequency bands will be trained during each session. Neurofeedback training will be performed on the EEG signal recorded from electrode position Cz against a right ear mastoid reference.
For the n-of-1 design of the trial, 2 participants will receive the SMR neurofeedback intervention and 2 participants will receive sham neurofeedback. Real and sham neurofeedback procedures will be similar (e.g., electrode position, preparation, instructions given to participants) except that for the sham neurofeedback training group, participants are instructed to enhance an irrelevant frequency band that is randomly chosen from higher beta bands (20-23 Hz, 23-26 Hz, 26-29 Hz, and 29-32 Hz). Therefore, no specific frequency band is systematically modulated and thus should not result in desired treatment outcomes. Participants will still be given positive feedback and be able to influence the video games in order to minimize possible irritation of participants. Neurofeedback will be applied as implemented within the BrainMarker software engine (BrainMarker Device, Brainmarker BV Gulpen). Participants will be shown simple video games implemented in the software that will provide feedback about their brain activity. During the video games, they are instructed to be attentive to the feedback (no movement/movement of objects) in the video game and to find the most successful strategy to reach the goal of the game. Example of such video games are a car moving on a road, where participants are instructed to keep the car in the right lane of the road, or a basketball court where participants are instructed to try to throw the ball in the basket. The video game-based neurofeedback rounds will last 1 minute at a time, with a short break in between rounds. Also, movie-based neurofeedback will be applied. During movie-based neurofeedback participants will watch a digital video disk of their own choice and be instructed to keep the monitor as free as possible from black curtains appearing on both sides of the monitor and keep the volume of the movie at an audible level. Movie-based training will last 90 seconds at a time with a short break when necessary. Participants will receive both game- and movie-based neurofeedback in each session.
Thresholds will be set manually in a way that if a participant maintains the reinforced frequency band above a threshold for 80% of time, positive feedback will be received. To determine threshold values, mean magnitude of the baseline measurement across the 3 conditions described above will be used to roughly assess threshold values for the neurofeedback training. For each training session, mean magnitude values will be calculated for all frequencies.

Statistical Analysis
All statistical analysis will be conducted using SPSS version 19 (IBM Corp). Summarizing descriptive statistics and frequency tables will be provided.

Randomized Controlled Trial. Resting state EEG data will be analysed using custom-made Matlab R2012b scripts (version R2012b). A repeated measures multivariate analysis of variance with factors condition (neurofeedback vs control) and frequency band (delta, theta, alpha, beta, or gamma) will be conducted. If main or interaction effects are observed, post hoc tests will be used to determine which levels of the factors are explaining the observed effects.
Repeated measurement with time (pre- [T0] and postintervention [T1]) as the within-subject factor and group (control vs intervention) as the between-subject factor will be conducted for the DAQ-SF, BIS-11, IFTE, and IFTE-SR. If main or interaction effects are observed, post hoc test will be used to determine which levels of the factors are explaining the observed effects. An repeated measures analysis of covariance will be conducted to examine differences in actual drug use as dependent variables to test for a moderating effect of impulsivity on craving and actual drug use.

N-of-1 Trial. First, a time-plot will be inspected using the autocorrelation coefficient (i.e., correlogram) (Chatfield, 2004) . After inspection, time-series analysis will be applied to test for significant slope and level changes as well as a trend analysis. Analysis techniques will be based on the study by Solanas, Manolov, and Onghena, 2010.

Results

Results of all measurements will be expected by the end of 2017 and will be published in corresponding articles.

Discussion

This study aims to evaluate the efficacy of an SMR-based neurofeedback treatment on reducing impulsivity in a population of inpatient forensic patients. Possible effects of a reduction in impulsivity on substance abuse will be assessed as well. We expect a significant reduction in impulsive behavior, level of craving, and actual drug use for participants receiving the SMR neurofeedback protocol. The n-of-1 approach might help to explain effects possibly found in the RCT study since it allows for a more direct focus on treatment effects by following participants closely and thereby being able to directly attribute behavioral and neurophysiological change to the SMR neurofeedback protocol employed. The study aims to extend previous findings on the efficacy of neurofeedback treatment in reducing impulsivity, not only by linking possible findings regarding a reduction of impulsivity to substance abuse symptoms but also by examining effects in a forensic psychiatric population with various comorbid disorders.
Studies about the efficacy of neurofeedback in a psychiatric forensic setting, in which the population is characterized by various comorbidities and various kinds of medication, are lacking. In our study, exclusion criteria are kept to a minimum to include as many participants with SUD as possible and to be able to generalize effects of an SMR neurofeedback treatment over different types of comorbidities.
Although RCTs with a treatment and a sham treatment arm are considered the gold standard in

research, conducting large trials is often times difficult in forensic settings; treatment motivation might be low for the type of patients in the treatment facility because they are placed under compulsory inpatient custody and are not seeking treatment due to inner motivation for change. In RCTs, number of participants usually has to be quite high to reach the desired effect size (Cohen, 1988). Participating patients might be even less inclined to take part in the trial if they know that they might end up in a placebo condition.

By employing an n-of-1 approach combined with an RCT, this study might help shed light on the underlying mechanisms of neurofeedback because an n-of-1 approach allows closer monitoring of treatment effects and provides valuable insight into an individual's treatment progress that might otherwise be lost in a between-group design (Rizvi & Nock, 2008).

If effective, neurofeedback could be a noninvasive treatment option for the reduction of impulsivity, which may lead to a reduction in feelings of drug craving and in actual drug use. Both impulsivity and drug-seeking behavior are known to hamper treatment progress and are strongly linked to criminal behavior (Stevens et al., 2014). By reducing impulsivity, chances of successful treatment for SUD may increase, thereby decreasing the risk for relapse in drug use and reducing criminal behavior.

There are several important issues to consider that might influence the results. First of all, participants are not selected based on their level of impulsivity. Even though the most commonly observed disorders in the treatment facility are schizophrenia and personality disorder and both types of disorders are associated with increased impulsive behavior, not all suitable participants might show elevated levels of impulsivity. Studies have shown that although there is evidence that heightened impulsivity can be found across different types of substance use disorders, there is still substantial heterogeneity on impulsivity levels within these groups (Verdejo-Garcia et al., 2008). A recent study by Albein-Urios et al. (2014) found several subgroups of addicted individuals that exhibited different clinical presentation and most interesting, different severity levels of craving. In the study, a latent class analysis showed that greater impulsivity levels were associated with worse clinical outcomes, whereas conventional diagnostic groups showed no significant differences on outcome variables. Also, there have been studies that show that antisociality is actually associated with better impulse control, independent of extent of drug use (Vassileva, Gonzalez, Bechara, & Martin, 2007). To ensure a sufficient number of participants, inclusion criteria in this study are quite lenient, which may provide heterogeneity within this sample. Ideally, participants would have to present with the same diagnoses, same type of medication, etc, however, this would limit the number of available participants to such an extent that it will be hard to find any effects. The heterogeneity of the population makes it possible that an impulsivity-based neurofeedback protocol might not result in a reduction of craving and actual drug use.

Also, participants will be included who have tested positive for drug use in the past 24 months. This implies that there will also be participants whose substance use disorder is in early remission. Although substance abuse–related symptoms such as craving are known to persist even after drug use is terminated, this period of time might be too long for these participants to report any craving at the moment of the administered questionnaire.

Chapter 4

The ability of forensic psychiatric patients with substance use disorder to learn neurofeedback

Published as: Fielenbach, Spreen, Donkers, & Bogaerts. (2018). The ability of forensic psychiatric patients with substance use disorder to learn neurofeedback. International Journal of forensic mental health.

Abstract

Despite the increasing use of neurofeedback in clinical psychology, it is rarely used in forensic psychiatric settings. This study investigated whether forensic psychiatric patients (n=19) diagnosed with substance use disorder were able to learn to control EEG-activity based on a sensorimotor rhythm/theta neurofeedback protocol. Criteria for qualifying patients as responders were established and scores on impulsivity measures and changes in level of craving over time were assessed. Results indicated that one in five patients was able to consistently change the targeted frequency bands. All patients improved on self-reported impulsivity measures and levels of craving, but only levels of craving were associated with responding to neurofeedback treatment. Patients were more able to up-train the sensorimotor rhythm magnitude than to down-train theta magnitude. Although these results are encouraging for some forensic patients, it is important to assess which patients will respond positively to the training and which will not. This requires more research.

Introduction

Neurofeedback training is increasingly used in clinical psychology as a noninvasive treatment method. With neurofeedback training, patients learn to regulate aberrant electroencephalographic (EEG-)activity assumed to underlie the manifestation of clinical and behavioral symptoms of various disorders. Since neurofeedback training aims directly at changing basic neurophysiological brain functioning, it is less dependent on direct patient-therapist interaction than traditional psychotherapeutic interventions (Casher, 2013). Patients' motivation and compliance for psychotherapy tends to be especially low in forensic psychiatric populations (O'Brien, & Daffern, 2017; Ogloff, Wong, & Greenwood, 1990). Neurofeedback training might provide a promising alternative treatment option for this patient population.

Forensic patients are often diagnosed with externalizing disorders characterized by lack of inhibitory control, such as Cluster B personality disorders, schizophrenia, and attention-deficit/hyperactivity disorder (ADHD). In addition, about 70% of the forensic patients have a comorbid substance use disorder (Van Nieuwenhuizen, Bogaerts, Ruijter, Bonges, & Coppens, 2011). In substance use disorder (SUD), lack of inhibitory control is especially pronounced. Drug-taking can be seen as a loss over control of drug-intake, despite the fact that people are usually aware of the negative consequences of their drug-use. Individuals with SUD show significantly higher score on various impulsivity measures, regardless of type of drug addiction (Fillmore & Rush, 2006; Nielsen et al., 2012). They show impaired response inhibition, which has often times already been observed in childhood and early adulthood (Hawkins, Catalano, & Miller, 1992). Individuals who report higher levels of impulsivity also report more frequent and more severe symptoms of SUD, such as the level of experienced drug craving. Studies in patients with methamphetamine (Tziortzis, Mahoney, Kalechstein, Newton, & Garza, 2011) or cocaine addiction (Moeller et al., 2001), as well as alcohol dependency (Joos et al., 2013), have shown that patients who score higher on impulsivity report more severe levels of craving.

For forensic psychiatric patients, the combination of SUD and comorbid major mental disorders also has a negative impact on treatment (Van Nieuwenhuizen et al., 2011), as high levels of impulsivity increase chances for relapse in substance abuse and treatment drop-out (Van der Veeken, Lucieer, & Bogaerts, 2016). Most likely, chronic substance abuse results in neurocognitive and neurophysiological changes, causing a structural state of reduced inhibitory control and high levels of impulsivity (Jentsch, & Taylor, 1999; Lyvers, 2000). Neurofeedback protocols aimed at enhancing the sensorimotor rhythm (SMR; 12-15 Hz) and reducing slower waves such as theta (3.5- 7.5 Hz) have shown promising results in reducing levels of impulsivity in (ADHD) (Fuchs et al., 2003). A reduction in levels of impulsivity through neurofeedback training could possibly also have a positive effect on SUD, as both impulsivity and SUD are characterized by a lack of inhibitory control (Tomko, Bountress, & Gray, 2016).

To our knowledge, neurofeedback training for forensic psychiatric patient populations with multiple externalizing disorders has not been performed so far. A possible explanation might be that comorbidity is often seen as a contra-indication to include patients in Randomized Controlled Trials (RCT's) (Janssen et al., 2017; Mayer, Blume, Wyckoff, Brokmeier and Strehl, 2016; Mayer, Wyckoff, Schulz, & Strehl, 2012; Mohammadi, Malmir, Khaleghi, & Aminiorani, 2015; Moreno-Garcia, Delgado-Pardo, Camacho-Vara de Rey, Meneres-Sancho, & Servera-Barcelo, 2015). Although neurofeedback training is increasingly applied in clinical populations, its effectiveness

is often solely described in terms of a reduction in behavioral and clinical symptoms (e.g., Bink, van Nieuwenhuizen, Popma, Bongers, & van Boxtel 2015). Results describing changes in deviant EEG-patterns due to neurofeedback training are often not reported.

A necessary first step in showing that clinical improvements are actually linked to successful regulation of cortical activity, is to demonstrate that learning of EEG-regulation has occurred during neurofeedback training (Gruzelier, Egner, & Vernon, 2006; Zuberer, Brandeis, & Drechsler, 2015). Previous research shows mixed results regarding the specific effects of neurofeedback training (e.g., Cortese et al., 2016; Zuberer et al., 2015), regardless of the applied neurofeedback protocol or the disorder for which the training was employed. Oftentimes, participants seem unable to learn to regulate the targeted cortical activity over the course of neurofeedback training. As an example, in a study among children diagnosed with ADHD, approximately 50% of participants were classified as so-called non-responders (Doehnert, Brandeis, Straub, Steinhausen, & Drechsler, 2008). Even in studies with non-clinical participants, responder rates tend to be quite low. Weber, Köberl, Frank and Doppelmayr (2011) trained non-clinical participants to increase SMR frequency through neurofeedback training. They found that only 43-54% of participants were able to consistently increase their SMR-frequency.

Studies describing learning progress during neurofeedback training have also reported different patterns of participants regarding the adaptation of learning strategies, with large inter-individual variability in learning performance (Drechsler et al., 2007; Leins et al., 2007; Strehl et al., 2006). Several studies (e.g., Bakhshayesh, Hänsch, Wyschkon, Rezai, & Esser, 2011; Lubar, Swartwood, Swartwood, & O'Donnell, 1995) report that participants showed positive learning curves at the beginning of a theta/beta neurofeedback training, followed by a stagnation in learning progress, again followed by a second learning curve at the end of the training sessions. This was similar to a Slow Cortical Potential (SCP) training protocol in a study by Mayer et al. (2016). The participants in this study showed a positive learning curve in the first few sessions, but then deteriorated and needed time to adapt strategies to deliberately control cortical activity. Inconsistent learning curves also add to the debate about the appropriate number of sessions required to see improvements, as studies vary significantly in the number of sessions (e.g., from 10 in schizophrenic patients (Gruzelier, Hardman, Wild, & Zaman, 1999) to 35-50 in ADHD (Gevensleben et al., 2009; Heinrich, Gevensleben, Freisleder, Moll, & Rothenberger, 2004). It is plausible that the complexity of comorbidity can complicate the learning process to regulate and control cortical activity.

This raises the question of (pre)conditions of neurofeedback training that must be met before starting an intervention among forensic psychiatric patients. Zoefel, Huster, and Herrmann (2010) have established three criteria that in their view any neurofeedback training should adhere to, in order to be valid: a) trainability: neurofeedback training should lead to effects in the trained frequency band b) independence: the training should not affect other frequency bands, and c) interpretability: frequency bands should be associated with certain cognitive functions to increase the probability of reliable behavioral effects.

The current study focuses on the trainability and interpretability aspect of neurofeedback training in forensic psychiatric patients with SUD, and other comorbidities, such as personality disorders, ADHD and/or schizophrenia. It will investigate: a) to what extent this patient group is able to learn to regulate neurophysiological activity through a theta/SMR-neurofeedback training, b) to what extent changes in frequency bands are related to changes in their levels of impulsivity, and

c) to what extent a reduction in levels of impulsivity is related to a reduction in their SUD related behavior, such as reduced levels of craving for substances and actual drug intake.

Methods

This study is part of a RCT investigating the effects of neurofeedback training for impulsivity in a forensic psychiatric population with SUD (Fielenbach, Donkers, Spreen, & Bogaerts, 2017). Results of the RCT will be reported elsewhere. In this study, only outcomes for those patients who received neurofeedback training will be reported. The study was conducted according to the principles of the Declaration of Helsinki (version 59, Seoul, October 2008) and in accordance with the Medical Research Involving Human Subjects Act. It has been approved by the medical ethical council of Brabant, the Netherlands (study number NL46390.008.13).

Participants

Participants were 26 forensic psychiatric patients residing in a maximum-secured inpatient treatment facility situated in Groningen, the Netherlands. Patients in this treatment facility are convicted for a crime with a minimum penalty of at least four years according to Dutch jurisdiction. These patients are held to be only partially responsible for their behavior due to mental illness and are admitted to a forensic psychiatric center by order of the state (called Ter Beschikking Stelling (TBS), Van Nieuwenhuizen et al., 2011). All patients suffer from at least one DSM-IV-TR disorder (American Psychiatric Association, 2000). Inclusion criteria for participants in this study consisted of at least one diagnosis of SUD according to DSM-IV-TR, and positive drug testing at the treatment facility in the past 24 months before the start of inclusion. Exclusion criteria were acute psychosis, acquired/congenital neurological brain disorders (e.g., epilepsy), and visual and/or auditory impairments, which would severely influence a patients' ability to follow neurofeedback training.

Patients were allowed to take medication during the study and clinical supervisors were asked to report pharmacological changes during the course of the training. Patients received 20 neurofeedback sessions, lasting 40 minutes at a time, two times a week. Neurofeedback training was added to treatment as usual (TAU). TAU was different for every patient, but typically consisted of cognitive behavioral therapy, non-verbal therapy (such as music therapy or psychomotor therapy), and behavioral skills training.

Before the start of the training, patients participated in pre-training measurements. After the last session, the same instruments were assessed again as post treatment-measurements.

Sample characteristics

Descriptive statistics are given in Table 1. Out of 26 patients, 19 patients completed all sessions of neurofeedback training. Patients dropped out due to transfers to different treatment facilities (n=1) or lack of motivation for the training (n=6). Patients who did not complete the training were excluded from further analysis. Although neurofeedback sessions were originally planned to take place two times a week resulting in a duration of 10 weeks of training per patient, due to the special setting in which this study took place, the intervention lasted for an average of 16.8 weeks (range 11-25, SD=4.86). Interruptions were due to patients not feeling well enough to complete

a training session, aggressive incidents which resulted in temporary separation/placement on a specialized crisis unit, unplanned furlough of patients, and lack of motivation to attend training sessions. Mean number of months in treatment by the start of neurofeedback was 95.3 months (range 22-247, *SD*=61.32). The large standard deviation was due to one patient who had already spent 247 months in treatment. Patients had an average of 4.6 (range 2-8, *SD*=1.64) DSM-IV-TR axis I and axis II disorders. The most common diagnosis on axis I was schizophrenia (*n*=10), and Antisocial Personality Disorder (*n*=7) and Personality Disorder Not Otherwise specified (PDNOS) (*n*=7) on axis II.

Measurements

Electroencephalography. For pre- and post-training measurements, participants received a five-minute resting state 21-channel eyes closed EEG measurement with Nexus-32 hardware and Biotrace+ software (Mind Media BV). The EEG was collected from 19 standard 10/20 positions (Herbert & Jasper, 1958), and the right and left mastoid with a sampling rate of 512 samples per second. The left mastoid served as the online reference. Flat type electrodes were placed above and below the left eye and at the outer canthi of each eye to be able to correct for vertical and horizontal eye movements. EEG magnitude across delta (0.5-3.5 Hz), theta (3.5-7.5 Hz), alpha (7.5-12 Hz), beta (12-20 Hz), SMR (12-15 Hz), high beta (20-32 Hz), and gamma (32-49 Hz) frequency bands was assessed.

Barratt Impulsiveness Scale-11 (BIS-11). The Dutch version of the BIS-11 (Lijffijt, & Barratt, 2005) is a self-report questionnaire designed to measure the behavioral and personality construct of impulsivity. It consists of 30 items and is scored on a four-point Likert scale ranging from 1 (rarely/never) to 4 (almost always/ always). The total score can be subdivided in three second-order factors: attentional, motor, and nonplanning. The BIS-11 has been shown to be an internally consistent measure of impulsivity among inmate populations (Cronbach's α=.80) (Patton, Stanford, & Barratt, 1995).

Modified Desire for Alcohol Questionnaire -Short Form (DAQ-SF). The Dutch version of the DAQ-SF (Franken, Rosso, & Honk, 2003) is a self-report questionnaire measuring the craving for alcohol at the moment of assessment. The short form of the DAQ consists of 14 items scored on a seven-point Likert scale, ranging from 1 (strongly disagree) to 7 (strongly agree). The DAQ-SF has shown to be a reliable measure to assess craving in a substance-dependent population (Cronbach's α=.70) (Courtney et al., 2013). All questions in the original version are designed to measure craving for alcohol, however, as the aim of this study was to measure craving for drugs in general, the word alcohol has been replaced by the word drugs. Patients were instructed to focus on their preferred drug of choice and indicate the level of experienced craving on the questionnaire. An extra written instruction was given, indicating that 'drugs' can refer to alcohol as well as soft- and hard drugs.

Substance abuse. To score substance abuse, the item 'substance abuse' on the risk assessment scale 'Historische, Klinische, Toekomst- Revised (HKT-R) (Historical, Clinical, Future-Revised) was used (Spreen, Brand, Ter Horst, & Bogaerts, 2014). The HKT-R is a clinical risk assessment instrument which was validated in a nation-wide population of forensic psychiatric patients

Table 1. Sample characteristics (N=19)

Sample			**Index offenses**	
				N
Age	Mean (SD)	38.31 (8.79)	Homicide	9
	Range	21.20-55.40	Violence	1
			Sexual offense	2
IQ	Range	72-101	Theft with violence	2
			Arson	1
Months in treatment			Extortion	4
Mean (SD)		95.26 (61.32)		
	Range	22-247		
Number of Axis I and II disorders				
Mean (SD)		4.63 (1.5)		
	Range	2-8		
	Diagnoses			
		N		N
Axis I			Axis II	
	Pervasive Developmental Disorder*[1]	2	Antisocial Personality Disorder	7
	Attention-deficit hyperactivity disorder (ADHD)*[2]	6	Borderline Personality Disorder	2
	Schizophrenia or other psychotic disorder	10	Personality Disorder Not Otherwise Specified	7
	Mood and Anxiety disorder	5	Avoidant Personality Disorder	1
	Cognitive impairment	2	Mental retardation	1
	Pedophilia	1		
	Other	1		
Substance use disorders				
	Alcohol	9		
	Cannabis	14		
	Amphetamines	4		
	Opioids	1		
	Cocaine	2		
	Diverse substances	5		
	Other	5		

**1 Pervasive developmental disorder: Autism, Aspergers disorder, developmental disorder not otherwise specified; *2 ADHD: All types of attention-deficit disorder; Index offense: In case of more than one index offense, the most serious one is reported, based on Nieuwenhuizen et al. (2011).*

(Bogaerts, Spreen, Ter Horst, & Gerlsma, 2018). This item is scored on a five-point scale ranging from 0 to 4. The items are scored as follows: 0- no drug use whatsoever, 1- the patient did not test positive for drug use, but did not cooperate with drug testing, 2- the patient had one positive drug testing, and might have also failed to cooperate with drug testing, 3- the patient tested positive for drug use at least twice, but did not refuse to cooperate with drug testing, and 4 – the patient tested

positive at least twice and also refused to undergo drug testing. The questionnaire differentiates between type of drug ('Soft drugs', 'Hard drugs', 'Alcohol' and 'Other'), and the item is scored on a five-point scale for each type of drug. The highest score on any of the different type of drugs is considered the final score. To score this item, results of regular drug testing as part of treatment facility policy were used. Positive drug testing is operationalized as any analysis testing positive for either marijuana, and/or psychostimulant/opioid drugs, and/or alcohol. Corresponding with treatment facility policy, non-prescribed medication that is used as recreational drug consumption such as inhaled Methylphenidate (e.g., Ritalin or Concerta), was also scored as a positive drug test, as well as refusal to undergo drug-testing. This item was scored weekly for the ten weeks prior to pre-training measurements, and for ten weeks after post-training measurements.

Cued Go/No-Go reaction time task. The cued Go/No-Go reaction time task is a measure of impulse control. It is a continuous performance task measuring the ability to inhibit a prepotent response (Fillmore, 2003). Participants sit in front of a computer, where blue and green squares are presented in five rounds with a short break in between. A total of 250 targets appear on the screen. Participants are asked to react as fast as possible to a green square but are instructed to inhibit a response when a blue square appears. A go or no-go cue appears before the target, indicating the likelihood of a green or blue target. The likelihood of a correct target is manipulated so that in 80% of the time the cue provides correct information and in 20% an incorrect cue is presented. Cues are presented with a fixed stimulus-onset interval (SOA) of 100, 200, 300 or 400 ms. Outcome measures are the number of commission errors, reflecting the failure to inhibit responses to no-go targets. The cued Go/No-Go reaction time task has been shown to be a valid measure of impulse control in a substance abusing population (Fillmore, 2003).

Intervention: Neurofeedback

A standard SMR-enhancement protocol was used, where SMR (12-15 Hz) was up-trained and theta (3.5-7.5 Hz) was down-trained (i.e., inhibited). If excess high beta (20-32 Hz) or delta (0.5-3.5 Hz) was detected, these frequency bands were inhibited as well, with a maximum of three frequency bands being trained in each session. Feedback training was performed on the EEG signal recorded from electrode position Cz against a right ear mastoid reference. Neurofeedback was applied as implemented in the Brainmarker software engine (BrainMarker Device, Brainmarker BV Gulpen). Every training session consisted of a number of feedback rounds, in which patients had to learn to control simple video-games by increasing and inhibiting the EEG signal in the desired frequency bands. Each round of video-game neurofeedback training lasted 60 seconds at a time with a short break in between rounds. Besides video-game based feedback, movie-based feedback was also given. Here, participants had to keep the monitor screen free from black curtains appearing over the displayed movie, resembling training parameter activity. Movie-based feedback lasted 90 seconds per round. Patients received positive feedback once a frequency band was maintained above or below a threshold for 80% of the time, depending on the frequency band that was enhanced or inhibited. Feedback thresholds were adjusted manually, based on how successful a patient was in regulating EEG-activity. During treatment sessions, patients were continuously encouraged to try their best and engage in the training. Positive verbal reinforcement was used whenever patients met feedback thresholds.

Data processing

As for the analysis of neurofeedback sessions, the last session (session 20) was excluded from the analysis. This session was usually combined with post-training measurements and therefore shorter in duration than the other sessions. Hence, data from session 1-19 were used for final analysis.

For each session of neurofeedback, standardized values for all frequency bands were calculated for every round of training. Absolute magnitude values at Cz were calculated per round of neurofeedback within the Brainmarker software and subsequently exported into SPSS. Magnitude values for frequency bands delta (0.5-3.5 Hz), theta (3.5-7.5 Hz), alpha (7.5-12 Hz), SMR (12-15 Hz), beta1 (12-18 Hz), beta2 (18-22 Hz), and gamma (22-30 Hz) were calculated. As the neurofeedback protocol consisted of up-training SMR magnitude while down-training theta magnitude, subsequent analysis focused on SMR and theta magnitude changes across sessions. Training rounds in which magnitude values differed more than two standard deviations from the mean were excluded, as these rounds were most likely influenced by artifacts due to eye blinking and/or movement. The resulting artifact free data were averaged, resulting in a mean and median magnitude per frequency band for each session.

Next, the total number of neurofeedback sessions was divided into time periods (TP). As Weber et al. (2011) argue, due to the high individual variability, no single session median value should be used for analysis, but median magnitudes across three consecutive sessions can be calculated as a so-called time period (e.g., TP2 is the median value of session two, three and four). As the analysis consisted of 19 sessions, 17 TP's were created. The median of SMR and theta magnitude of each TP was calculated. Before beginning of the actual training, a one-minute baseline EEG measurement with eyes-closed and eyes-open was performed. However, as cognitive demands required by neurofeedback tasks are quite different from an eyes-open or eyes-closed resting state, it can be argued that these measures do not reflect patients' baseline median frequency magnitudes adequately. Therefore, TP1 (consisting of the median value of sessions one, two and three) was chosen to serve as the baseline.

Criteria for establishing neurofeedback responders vs non-responders

This study adapted part of the criteria set out in the study by Weber et al. (2011) for the definition of (non-) responders. They argued that, for responders, a) EEG magnitudes should change in the desired direction during all training sessions, resulting in a positive mean magnitude change across all sessions, and b) the increase of mean percentage of EEG magnitude during the training should exceed 8% by the end of training as compared to the baseline state. The increase of 8% or higher given by Weber et al. (2011) was based on their clinical experience, where less than half of the subjects were able to gain a 10% increase in the investigated frequency band. However, since Weber's et al. developed these criteria based on non-clinical participants, it can be expected that forensic patients have more difficulties in learning to regulate cortical activity and may not achieve magnitude changes in the desired direction during every single session. Therefore, these criteria were somewhat adjusted to fit the population of this study. The definition of neurofeedback responders for this study was as follows:

1. Mean magnitudes of theta and SMR should change in the desired direction for 60% of all training sessions. In this study, 19 sessions of neurofeedback training were used for analysis, resulting in a minimum of 11.4 sessions (we will use 11 sessions). As the neurofeedback protocol

applied consisted of downtraining theta while simultaneously uptraining SMR frequency, in order to be qualified as neurofeedback responders, patients had to show a change in both frequency bands during at least eleven sessions. To test for possible differences between frequency bands (e.g., that patients find the regulation of one frequency band easier than regulation of the other), number of sessions in which only SMR magnitude increased were investigated separately, as were training sessions in which only theta magnitude decreased.
2. Overall, participants had to show an average change in EEG magnitude of 8% in the desired direction (increase of SMR/decrease of theta) by the end of the training as compared to baseline. This criterion proposed by Weber et al. (2011) was not adjusted for the current patient population, as it can be argued that an average change in EEG magnitude of less than 8% might not be clinically relevant anymore.
In order for patients to be qualified as neurofeedback responders, both criteria had to be met. Next, percentage increase/decrease of median values for each TP relative to baseline was calculated, as well as average increase/decrease over all time periods.

Statistical analysis

To test for changes between pre- and post-training, a Wilcoxon signed-ranks test was performed for behavioral measures DAQ-SF, BIS-11, and Cued Go/No-Go reaction time task.
Multiple linear regression analyses were performed to investigate whether successful regulation of frequency bands could predict changes in the dependent variables BIS-11, DAQ-SF, and commission errors on the cued Go/No-Go reaction time task. For each behavioral measure, two regression models were computed. In the first model, the post-training score was predicted by the pretraining score to determine the percentage of variance of the post-training score that was already explained by the pretraining score. In the second model, the successful regulation of SMR and theta magnitude for 11 or more sessions, the average increase of SMR magnitude and the average decrease of theta magnitude were added subsequently and evaluated by a partial F-test to statistically decide whether this addition contributed significantly to the increase in explained variance.
To test for changes in actual drug use, scoring of the item ‘substance abuse’ of the HKT-R was averaged for the weeks prior to training and the weeks after the training. A paired-sample t-test was performed to test for changes in drug use.
Spearman’s rho correlations were performed to assess whether the number of times patients successfully achieved up- or down-regulation in the desired direction was correlated with the height of average increase or decrease in the frequency band. Spearman correlations were also calculated for outcomes on BIS-11, DAQ-SF, amount of commission errors on the Cued Go/No-Go reaction time task and performance during neurofeedback.
All data were analyzed with SPSS version 22 (IBM Corp).

Results

Responder versus non-responder

Results with regard to responding vs non-responding to neurofeedback training were analyzed in multiple ways. Results are given in Table 2.

1. The first criterion for being a neurofeedback responder stated that the patient showed magnitude changes in the desired direction of frequency bands for at least 60% of the 19 sessions, resulting in magnitude changes during a minimum of 11 sessions. When inspecting sessions in which patients successfully decreased theta magnitude while also simultaneously increasing SMR magnitude, only 4 out of 19 patients (21%) were able to do so for 11 or more sessions. So, according to criterion one, only 4 out of 19 patients could be qualified as a neurofeedback responder.

To test for differences between frequency bands, sessions in which only theta magnitude changed or only SMR magnitude changed, were also investigated. When inspecting mean decrease in theta magnitude, 7 out of 19 (37%) patients were able to decrease their theta magnitude during 11 sessions or more. For increases in SMR magnitude, 12 out of 19 (63%) patients managed to consistently increase SMR magnitude in 11 or more sessions.

2. The second criterion for establishing neurofeedback responding stated that, next to an magnitude change in the desired direction for 11 or more sessions, the average magnitude change had to exceed 8%. When inspecting magnitude change in the SMR frequency over all sessions, all 4 responders showing magnitude changes in the desired direction achieved an average increase

Table 2. Achieved treatment success in frequency bands and average increase/decrease in frequency bands over time periods per patient (N=19).

Patient	Number of times SMR up	Number of times theta down	Number of times SMR up AND theta down	Average change in SMR in %	Average change in theta in %
1	4	6	0	-4.8	1.5
2	15	1	0	2.3	5.5
3	0	0	0	-5.3	5.1
4	5	3	0	-2.9	2.5
5	6	0	0	-2.0	12.9
6	0	16	0	-24.0	-12.1
7	7	0	0	-1.8	10.3
8	17	0	0	18.4	13.7
9	3	5	0	-3.1	8.0
10	17	6	5	13.5	4.1
11	16	14	10	4.7	-11.9
12	12	11	6	2.3	-1.3
13	17	8	8	19.1	-.73
14	17	6	5	15.4	1.8
15*	17	16	16	12.2	-8.5
16*	15	16	14	15.3	-11.4
17*	17	15	15	9.5	-8.7
18*	17	15	14	26.0	-6.7
19	17	5	4	19.0	1.4

in SMR magnitude of 8% or higher (range 10%-26%). For theta, 3 of 4 responders showed an average magnitude decrease of 8% or more (range 8%-11%).
Average increase in SMR magnitude of 8% or higher (range 13%-19%) could also be observed for patients who did not manage to simultaneously decrease theta magnitude for 11 or more sessions, but who still managed to increase only SMR magnitude for 11 or more times (*n*=7),

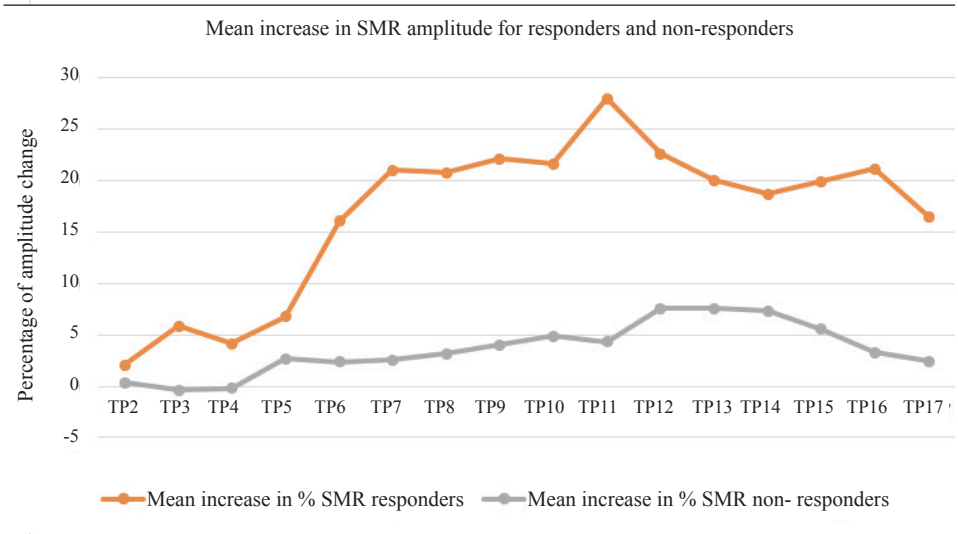


Figure 1. Percentage of SMR amplitude change in % for TP 2 - TP 17 for responders versus non-responders.

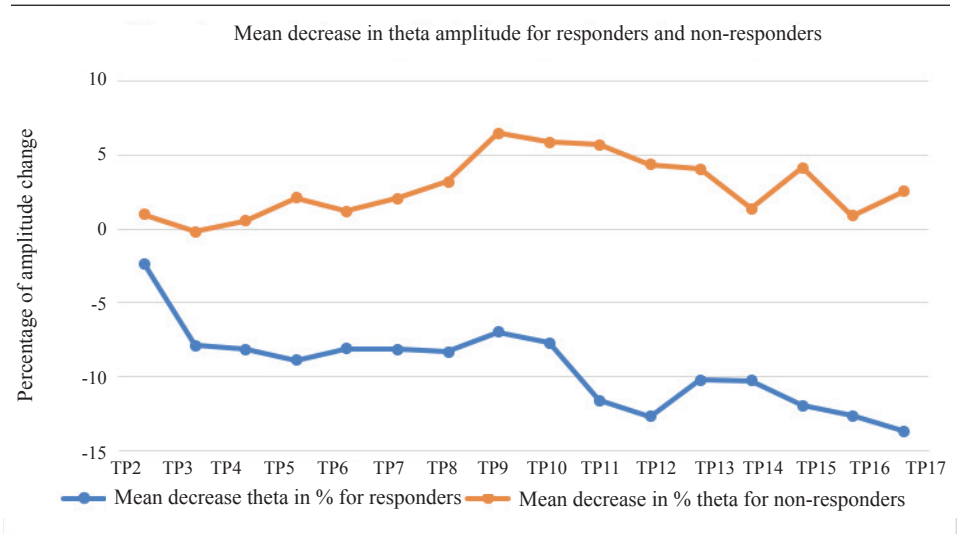


Figure 2. Percentage of theta amplitude change in % for TP 2 - TP 17 for responders versus non-responders.

except for two patients. For theta magnitude, this was the case for only two patients.
Patients that could not be classified as a responder seemed unable to learn to regulate the targeted EEG-frequencies in the required direction. About a third of the patients (6 out of 19 patients (32 %)) showed an increase in magnitude where a decrease was desired, and/or vice versa.
Responders showed a steeper learning curve of SMR magnitude increase than non-responders. For theta magnitude, only responders showed a stepwise decrease in theta magnitude while theta magnitude of non-responders fluctuated but remained flat over all 17 TP's.
Figures 1 and 2 show the mean increase in SMR and theta magnitude for responders and non-responders over all 17 TP's. Responders showed a steeper learning curve of SMR magnitude increase than non-responders. For theta magnitude, only responders showed a stepwise decrease in theta magnitude while theta magnitude of non-responders fluctuated but remained flat over all 17 TP's.
Spearman's rho correlations between number of times patients successfully achieved up- or downregulation in the desired direction and height of average increase or decrease in the frequency band was significant at the $\alpha<0.01$ level in a single frequency (either theta or SMR) (theta: $r=-.972$, $p<.01$; SMR: $r=.924$, $p<.01$), as well as for the number of times SMR and theta were successfully regulated simultaneously (number of times SMR and theta were regulated simultaneously and average success SMR $r=.619$, $p<.005$, number of times SMR and theta were regulated simultaneously and average success theta $r=-.697$, $p<.001$) for the total patient group.

Behavioral measures

A Wilcoxon Signed-ranks test indicated that results on the BIS-11 and DAQ-SF were significantly lower post-training (BIS-11: $Z=-2.2$, $p<0.05$, $r=-.5$; DAQ-SF: $Z=1.982$, $p<0.05$, $r=.45$) for the whole group of patients. Commission errors on the Cued Go/No-Go task did not show significant changes between pre and post-training ($Z=-.6$, $p>0.05$, $r=-.14$).
A paired sample t-test showed that there was a significant difference ($p<0.05$) in degree of positive drug testing post-training ($M=.29$, $SD=.43$), indicating a decrease in positive drug testing post-training.

Table 3. Multiple regression with results of DAQ-SF post-treatment as dependent variable in model 1, and the average increase of SMR amplitude as predictor in model 2 (N=19).

Model		Unstandardized coefficients		Standardized coefficients	T	Sig.
		B	*SE B*	*B*		
	(Constant)	12.54	8.65		1.45	.17
1	DAQ-SF T0	.51	.20	.53	2.60	.02
2	(Constant)	18.27	8.13		2.25	.04
	DAQ-SF T0	.45	.18	.47	2.52	.02
	Average increase SMR	-.53	.23	-.43	-2.29	.04

R2 Model 1 = .28
R2 Model 2 = .46; Fpart = .04
Note: The t-test in model 2 is identical to the partial F-test, as there is only one variable added as compared to model 1.

Separate multiple linear regression analyses were performed to investigate results on DAQ-SF, BIS-11, and number of commission errors post-training based on various responding criteria. Only significant results are reported, see Table 3 for results.

Discussion

To the best of our knowledge, this is the first study that employed an theta/SMR frequency neurofeedback protocol in forensic psychiatric patients with SUD and co-morbidities. It was investigated whether this complex group of patients is actually able to consistently regulate SMR and theta frequency band activity during a 20 session neurofeedback training and whether changes in these frequency bands were related to changes in level of impulsivity, craving, and actual drug use.

Patients were categorized as responders when they showed both a successful upregulation of SMR magnitude and a successful downregulation of theta magnitude during at least 11 out of 19 sessions and showed an average increase/decrease in the desired direction of 8% or higher. Despite the fact that personality measures of impulsivity, level of craving for addictive substances, and degree of positive drug testing were significantly lower post-training than pre-training on a group level, only 4 out of 19 patients (21%) could be categorized as a responder to the neurofeedback training. The low number of patients who achieved a responder status was mainly due to the low number of patients who managed to consistently decrease theta, as the number of times patients successfully achieved up-training of SMR magnitude was much higher. Subsequent analysis showed that the ability to consistently train frequency bands in the desired direction was not related to scores on impulsivity measures post-training. Levels of craving post-training could partially be explained by whether patients could be categorized as responders, but were only related to the increase in SMR frequency and not to a decrease in theta frequency.

Zuberer et al. (2015) differentiate between 'EEG-learning' (comparable to the trainability criterion by Zoefel et al., 2011) and 'EEG-training response'. EEG-learning refers to the improvement in a targeted cortical training parameter in the desired direction, whereas 'EEG-training response' refers to any change in neurophysiological parameters due to neurofeedback training. The results of the current study showed that although all patients showed an EEG-training response, only a fifth of patients showed EEG-learning. This can be considered quite a low number. The difficulties patients seem to experience in downregulating theta as opposed to upregulating SMR activity have been observed in studies with other populations as well. Doppelmayr and Weber (2011) showed that non-clinical individuals were able to increase SMR frequency over the course of training, but failed to decrease the theta/beta ratio. Janssen et al. (2017) employed a theta/beta neurofeedback protocol in children with ADHD, and found theta to remain unchanged during the course of training when inspecting results on a group level, whereas a linear increase was observed for beta activity. However, when investigating individual learning curves in the study by Janssen et al. (2017), the number of participants that could be qualified as responders was much higher than that in the current study: 39% of participants could be qualified a responders with regard to theta, and 53% of participants could be qualified as responders with regard to beta. Research on which patients will be able to benefit from neurofeedback training in terms of EEG-training response is still in its infancy. Therefore, no adequate comparisons can be made

with regard to whether 21% of participants is a good representation of EEG-learning abilities in the current patient population. Janssen et al. (2017) also investigated individual learning curves of participants and found that 18% of participants displayed a change of theta in the opposite direction over the course of training whereas only 8% of patients showed a change of beta in the opposite direction. In the current study sample, the number of participants showing learning curves in the opposite of the intended direction was also much higher: 58% of patients actually increased their theta magnitude as opposed to decreasing it, whereas 36% patients decreased SMR as opposed to increasing it. With only one in five patients being able to achieve EEG-learning, it is questionable whether this intervention will actually be able to lead to clinically significant improvements for a sufficient number of patients.

Several studies have suggested that training outcomes might depend on the number of frequency bands trained, with a negative correlation between the number of trained frequency bands and training success (Rogala et al., 2016). Especially when EEG-frequency bands are adjoining and effects in one frequency might be susceptible to training effects in another frequency band, this could pose a problem. However, SMR and theta frequency bands seem sufficiently far separated from one another to prevent that upregulation in one band is cancelled out by the down-regulation of the other. It might be possible, however, that for this specific patient population, the training of two frequency bands simultaneously is just too difficult. Future studies with this patient population might benefit from neurofeedback training that is focused solely on enhancing SMR frequency, since improvements on craving measures in this study were related to an increase in SMR magnitude specifically.

Another possible explanation for the low number of responders might be the fact that patients were allowed to continue using prescription medication during the course of the study. It can be considered unethical to ask patients to stop taking medication for the sake of an intervention for which efficacy is not yet established. However, to date, the effects of medication on the trainability of EEG-frequency bands are unclear. It is possible that the effects of medication might 'overrule' training effects of neurofeedback. Previous research has shown that stimulant medication can produce a normalization of relative power in the theta band frequency in the resting-state EEG of patients with ADHD (Clarke et al., 2003). It is possible that patients with this type of medication might not be able to further normalize theta frequency through neurofeedback. Nonetheless, even if stimulant medication prevents patients from further decreasing their theta-frequency power, additional research is needed to investigate why more than half of the patients in the current study increased their theta frequency when the neurofeedback protocol was aimed at decreasing it.

Future studies need to assess the specific effects of neurofeedback training on the modulation of other EEG-frequency bands in forensic patients, as well as the necessary number of sessions to achieve optimal clinical results. It is possible that more patients would have been classified as responders if more than 20 training sessions had been applied. Strehl et al. (2006) argue that it is not a necessity for participants to show a positive learning curve over each individual session, as some participants might not find an optimal strategy until the end of the training. At the same time, it is of great importance to be able to predict as early as possible in the process which patients will be able to benefit from neurofeedback and which will not. Especially for vulnerable patient populations like forensic psychiatric patients, who are already difficult to engage in therapy as it is, it is important to be able to decide as quickly as possible whether they are likely to benefit from a neurofeedback training in order to not burden them with a therapy modality that they might not be able to benefit from.

Limitations

This study did not investigate within-session learning curves of patients. This makes it difficult to interpret results in terms of whether patients were actually able to regulate frequency bands within each session, and to draw conclusions on whether other mechanisms are involved that lead to the consolidation of cortical changes across sessions. Furthermore, it is important to note that, although 21% of patients did show neurofeedback training responses in the desired direction and, as a group, improved on self-report measures of impulsivity and levels of craving, the lack of a sham neurofeedback condition makes it difficult to rule out the possibility of a placebo effect. Furthermore, although participants were continuously encouraged to try their best and engage in neurofeedback training, it cannot be ruled out that some patients were not trying as hard as others. This is a general problem with neurofeedback training. There is no way to be absolutely certain that a patient really does focus on the training, or is just pretending to do so. In the current study, patients in the treatment facility did not receive more privileges due to participating in the study, and it can be argued that it is too hard and possibly too boring to just sit and stare at the monitor for twenty neurofeedback sessions. Seven patients dropped out during the course of the study, of which six patients dropped out due to lack of motivation. However, given that patients did receive a financial reward for participation, it is possible that some patients pretended to engage in the training in order to receive a financial compensation. This could be tackled by the use of a sham neurofeedback condition in future studies.

Another limitation is the use of a modified version of the DAQ-SF. While the DAQ-SF itself has good reliability, the modification made to the questionnaire may have influenced the validity and reliability of the questionnaire to some extent.

Another limitation concerns the way the HKT-item 'substance abuse' has been assessed. While the questionnaire differentiates between types of drugs ('Soft drugs', 'Hard drugs', 'Alcohol' and 'Other'), the scoring itself does not, as the scoring is based on the highest score given for any of the different types of drugs used. Therefore, the questionnaire is not able to detect changes in type of drug used. In SUD, substance abuse often times is not limited to one specific type of drug, but in many cases concerns polydrug abuse. It can be argued that a patient's efforts to refrain from using hard drugs such as cocaine is a huge step in the recovery process, even though certain type(s) of soft drugs such as marijuana are still used. With the questionnaire employed in this study, this type of change could not be assessed.

Conclusion

In conclusion, the trainability aspect of an theta/SMR neurofeedback training for forensic psychiatric offenders with SUD could partially be validated, as 21% of patients were able to regulate cortical activity in the desired direction. This study shows the importance of intervention sensitivity and assessment of responders and non-responders to the applied neurofeedback protocol. Additional research is needed to examine possible placebo effects of neurofeedback training and to establish criteria that can predict within a few neurofeedback sessions which patients will likely be able to benefit from neurofeedback and which patients will most likely not benefit from this type of intervention.

Chapter 5

Effects of a theta/sensorimotor rhythm neurofeedback training protocol on measures of impulsivity, drug craving, and substance abuse in forensic psychiatric patients with substance abuse: randomized controlled trial

Published as: Fielenbach, Donkers, Speen, & Bogaerts (2018). Effects of a Theta/Sensorimotor Rhythm Neurofeedback Training Protocol on Measures of Impulsivity, Drug Craving, and Substance Abuse in Forensic Psychiatric Patients With Substance Abuse: Randomized Controlled Trial. JMIR Mental Health, Dec 11;5(4):e10845

Abstract

Forensic psychiatric patients are often diagnosed with psychiatric disorders characterized by high levels of impulsivity, as well as comorbid substance use disorders (SUD). The combination of psychiatric disorders and SUD increases the risk of future violence. Chronic substance abuse can lead to a structural state of disinhibition, resulting in more drug taking and eventually loss of control over drug intake. When treating SUD, it is crucial to address high levels of impulsivity and lack of inhibitory control. The current study set out to investigate the effects of a theta/sensorimotor rhythm (SMR) neurofeedback training protocol on levels of impulsivity, levels of drug craving and actual drug intake in a population of forensic psychiatric patients with a diagnosis of SUD. 21 participants received 20 sessions of theta/SMR neurofeedback training in combination with treatment as usual (TAU). Results were compared to 21 participants who received TAU only. SMR magnitude showed a significant (p=.02) increase post-training for patients in the neurofeedback training group, whereas theta magnitude did not change (p>.05). Levels of drug craving, as well as scores on the 'motor' subscale of the BIS-11 decreased equally for patients in the neurofeedback training group and the TAU group. Other measures of impulsivity, as well as drug intake, did not change post-treatment (p>.05). Therefore, neurofeedback + TAU was not more effective than TAU only. The current study demonstrated evidence that forensic *p*sychiatric patients are able to increase SMR magnitude over the course of neurofeedback training. However, at the group level, the increase in SMR activity was not related to any of the included impulsivity or drug craving measures. Further research should focus on which patients will be able to benefit from neurofeedback training at an early stage of the employed training sessions.

Introduction

Forensic psychiatric patients are often times diagnosed with disorders characterized by high levels of impulsivity. Schizophrenia, attention-deficit hyperactivity disorder (ADHD) and cluster B personality disorders are the most common disorder in forensic psychiatric patients (Schuringa, Heininga, Spreen, & Bogaerts, 2018; Simpson, Grimbos, Chan, & Penny, 2015). Substance use disorder (SUD) is a common comorbidity, occurring in a about 55-70% of all patients (Simpson et al., 205; Van Nieuwenhuizen, Bogaerts, Ruijter, Bonges, & Coppens, 2011).

Individuals abusing alcohol, stimulants and opioids tend to have higher levels of impulsivity as compared to non-abusing controls (Loree, Lundahl, & Ledgerwood, 2015). Furthermore, impulsivity is a risk factor for the development and maintenance of SUD (Hawinks, Catalano, & Miller, 1992; Charney, Zikos, & Gill, 2010). Chronic substance abuse can cause a structural state of disinhibition over time, leading to permanent excessive abuse of substances (Jentsch & Taylor, 1999; Lyvers, 2000; Crews & Boettiger, 2009). This state is not limited to the acute stages of substance dependency, but is also present in patients after stopping regular drug intake (Roozen, van der Kroft, van Marle, & Franken, 2011). Elevated levels of impulsivity are also associated with more severe symptoms of SUD, that eventually lead to higher levels of drug craving (Bornovalova, Levy, Gratz, & Lejuez, 2010). Once patients receive substance-abuse treatment, high levels of impulsivity can increase chances of early relapse and premature termination of treatment (Charney et al., 2010; Roozen et al., 2011). For forensic psychiatric patients, substance use is highly associated with the use of violence, regardless of the type of drug used (e.g., (Boles & Miotto, 2003; Alniak, Erkiran, & Mutlu, 2016; Dugré, Dallazizzo, Giguère, Potvin, & Dumais, 2017).

Important in the treatment of forensic patients with SUD is to determine levels of impulsivity and lack of inhibitory control. In accordance with this, common psychotherapeutic approaches for SUD involve the adaptation of strategies that promote conscious decision making, attention to action and control over behavior (Crews & Boettiger, 2009). Despite that, relapse rates following remission of treated SUD individuals are as high as 60% (Marissen, Franken, Blanken, van den Brink, & Hendriks, 2009), stressing the need for additional interventions.

In the last two decades, electroencephalographic (EEG-)neurofeedback training has shown promising results in reducing high levels of impulsivity in patients suffering from ADHD (Zuberer, Brandeis, & Drechsler, 2015; Fuchs, Birbaumer, Lutzenberger, Gruzelier, & Kaiser, 2003; Arns, Drinkenburg, & Kenemans, 2012). Neurofeedback training uses real-time EEG measurements and displays this information back to the patient (Sokhadze, Stewart, Tasman, Daniels, & Trudeau, 2011). EEG-neurofeedback training works by enhancing or inhibiting brain frequencies that have shown to underlie abnormal psychological states (Gunckelman, & Jonhstone, 2005). An often used neurofeedback protocol to train impulse control is the so-called theta (3.5 Hz- 7.5 Hz)/ sensorimotor rhythm (SMR, 12-15 Hz) protocol (e.g., Fuchs et al., Rossiter & LaVaque, 1995; Monastra, Lynn, Linden, Lubar, Gruzelier, & LaVaque, 2005). In this protocol, the magnitude of the SMR frequency is enhanced, while the magnitude of the theta frequency is inhibited.

However, the effectiveness of a theta/SMR based neurofeedback protocol on levels of impulsivity and also on symptoms of SUD, such as levels of craving and actual drug use in forensic psychiatric patients is unclear. Only a few studies have investigated the effects of neurofeedback training in forensic psychiatric patients (e.g., Konicar et al., 2015; Martin & Johnson, 2005; Smith & Sams, 2005; Quirk, 1995). Therefore, investigating effectiveness of neurofeedback training can add

value to treatment models that are currently used for this group, such as classical psychotherapy and pharmacological treatment.

The primary objective of the current study was to examine to what extent a theta/SMR based neurofeedback training results in the reduction of impulsivity, drug craving and actual drug use in a population of forensic psychiatric patients with a diagnosis of SUD. Patients participated in 20 sessions of a theta/SMR neurofeedback training protocol in addition to treatment as usual (TAU). Levels of impulsivity, as measured with the Barratt impulsivity Scale-11 (BIS-11) (Lijffijt & Baratt, 2005) and a cued Go/No-Go reaction time task (Fillmore, 2003) were assessed. Levels of drug craving were measured with a modified version of the Desire for alcohol questionnaire (DAQ-SF) (Franken, Rosso, van Honk, 2003). Actual drug intake was assessed with urine or breathalyzer drug testing. Results on primary outcome measures were compared to patients from a control group who received TAU only. We hypothesized that patients receiving neurofeedback training + TAU would show reduced levels of impulsivity post-training, as well as a reduced levels of drug craving and drug use in comparison to patients receiving TAU only.

Method

Study design and participants

This study reports the results from a randomized controlled trial (RCT) as described in (Fielenbach, Donkers, Spreen, & Bogaerts, 2017). The results of the n-of-1 clinical case series are reported in Fielenbach, Donkers, Spreen, Smit, & Bogaerts (under review).

The study took place in a maximum security inpatient forensic psychiatric center (FPC) in Groningen, the Netherlands. All patients in this treatment facility are male criminal offenders, who were held only partially responsible for the crime they committed due to severe mental illness, according to Dutch jurisdiction (van Marle, 2002). Inclusion criteria were the presence of at least one DSM-IV-TR (American Psychiatric Association, 2000) diagnosis of SUD, positive drug testing in the past 24 months before inclusion, and sufficient knowledge of the Dutch language to understand training instructions. All patients had at least one comorbid axis I and/or II diagnosis. Exclusion criteria were a state of acute psychosis, in which patients experienced severe delusions and/or hallucinations and could possible become a threat to themselves or others (a diagnosis of schizophrenia, as well as disorders in the schizophrenia spectrum (e.g., schizoaffective disorder) were not considered exclusion criteria). A comorbid diagnosis of epilepsy; and visual and/or auditory impairments, which would hamper patients' ability to follow instructions and adhere to the neurofeedback training were also exclusion criteria. Medication intake was not restricted. Patients were allowed to continue the use of medication over the course of the study. Treatment supervisors were informed that, during the course of the study, prescribed medication should preferably remain stable, and that a change in type as well as dosage of medication should not be made during the course of the study unless absolutely necessary. Treatment supervisors were asked to inform researchers in case a change in type or dosage of medication did occur.

This study was conducted according to the principles of the Declaration of Helsinki (version 59, Seoul, October 2008) and in accordance with the Medical Research Involving Human Subjects Act. It is ethically approved by the medical ethical council of Brabant, the Netherlands (study number NL46390.008.13).

Procedure

In this study, a pre-post-test design was used. A power analysis calculation for the RCT, using G*Power 3 based on a 1-tailed alpha value of .05, a power value of 0.80, and an effect size (*f*) of 0.80 yielded a recommended sample size of 21 participants each in the control and intervention conditions.

Out of all participants that met the requirements, a random sample was drawn and randomly assigned to one of the two study conditions (neurofeedback training + TAU or TAU only). Patients were approached through treatment supervisors for participation and informed about the general outline of the study. If they expressed interest in participating in the study, they were approached by one of the researchers to explain the study design and randomization procedure. All patients signed the informed consent. Randomization was done by a random number generator. See Figure 1 for an overview of patient flow through the study.

Participants in both conditions underwent pre-treatment measurements (T0), consisting of the measurements described below. Participants in the control group received TAU only. TAU was different for every patient, as treatment modalities are based on individual diagnosis and problematic behavior of the patient, as well as the cognitive ability to undergo different treatment modalities. Examples of treatment modalities were non-verbal therapy forms (e.g., psychomotor therapy, musical therapy) and cognitive-behavioral group therapy. After 10 weeks, participants in the control group underwent post-treatment measurements (T1), identical to pre-treatment measurements.

Once pre-treatment measures were completed, participants in the intervention group started the neurofeedback training. They received 20 neurofeedback training sessions, scheduled two times a week for 10 weeks. Neurofeedback training was done by a certified neurofeedback therapist. The study was not blinded, as it was clear to patients as well as the neurofeedback therapist which patients received the neurofeedback training.

Participants received a small financial compensation comparable to minimum wage in the treatment facility for participation.

Neurofeedback training protocol

For neurofeedback training, electrode Cz was used as the feedback electrode recorded with Ag/AgCl electrodes against a right ear mastoid reference and a FPz ground electrode. Neurofeedback was applied as implemented in the Brainmarker software engine (BrainMarker Device, Brainmarker BV Gulpen). A theta/SMR protocol was used, in which SMR (12-15 Hz) should be enhanced and theta (3.5-7.5 Hz) should be inhibited. If excess high beta (20-32 Hz) or delta (0.5-3.5 Hz) was detected, these frequency bands were inhibited as well, with a maximum of three frequency bands being trained in each session. Patients were shown simple video-games and instructed to find the most successful strategy to make the main character of the video game move. A movie-based neurofeedback paradigm was given as well, where patients had to stop black 'curtains' from appearing over the computer monitor. The software provided visual positive feedback for increasing SMR magnitude and decreasing theta magnitude. Each round (or trial) of video-games lasted 60 seconds, with short breaks in between rounds (trials). Movie-based feedback lasted 90 seconds at a time. The switch between video- and movie-based feedback was done in order to make neurofeedback more fun and less tiring, as choice of video games provided within the software was limited, as well as very simplistic. For each patient, about ten rounds

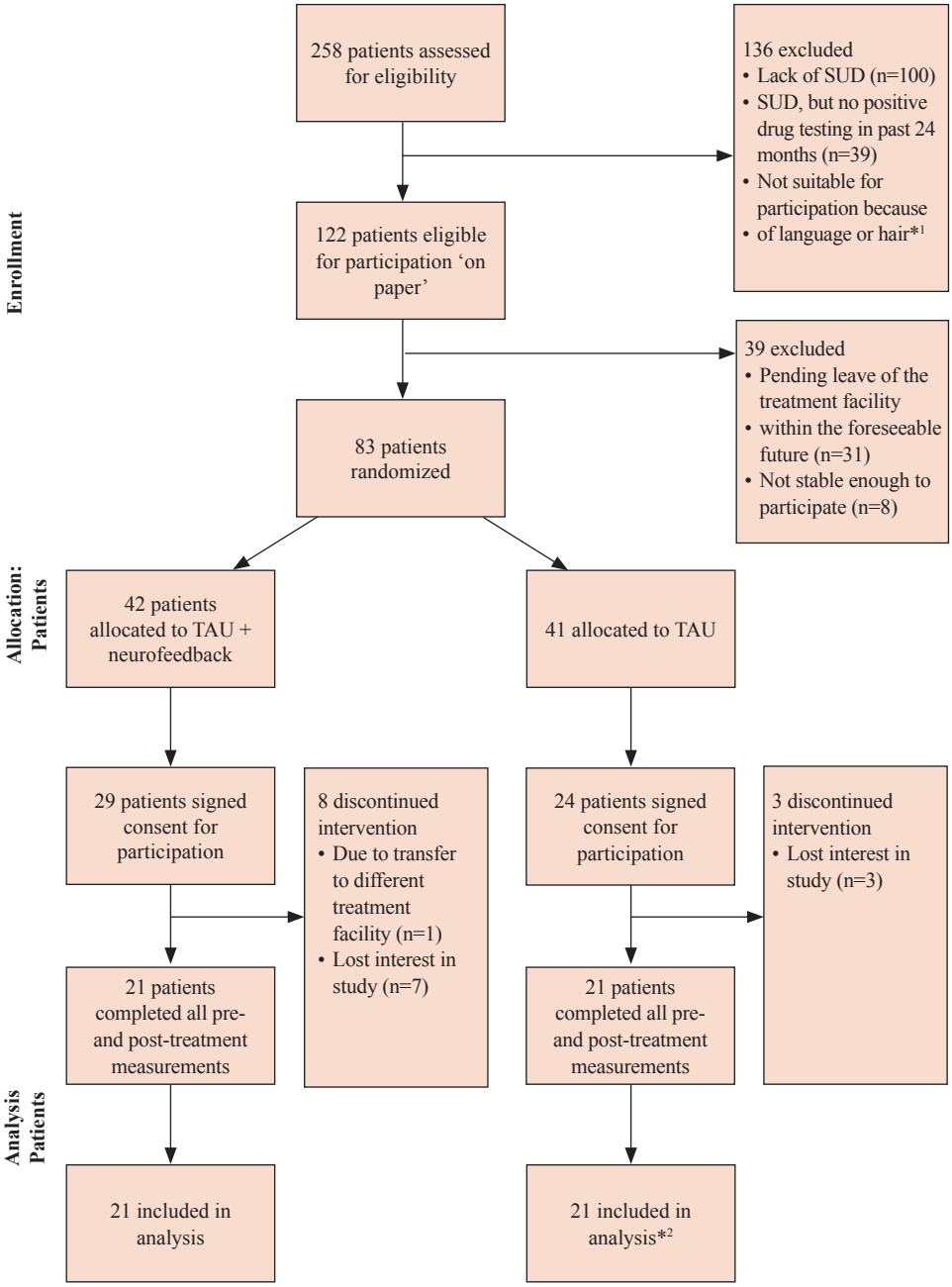


Figure 1. CONSORT flow diagram for individual randomized controlled trials of nonpharmacologic treatments.
**1 Patients who had hair that would was unsuitable for conducting EEG measurements or placement of neurofeedback electrodes, such as dreadlocks.*
**2 For analysis of drug testing, data from 19 patients was used.*

of video game-based feedback were employed. As for movie-based feedback, about 10 to 15 rounds were employed. Neurofeedback training lasted for approximately 45 minutes, including preparation and clean-up.

Feedback thresholds were adjusted manually whenever participants were able to increase or decrease the desired frequency bands for 80% of the time. Participants were verbally encouraged to try to move the main character in the video game as much as possible, as well as to keep to monitor free from the curtains during video-based feedback and not just stare at the screen. See Figure 2 for an impression of one of the neurofeedback games. After all training sessions were completed, participants underwent post-treatment measurements (T1).

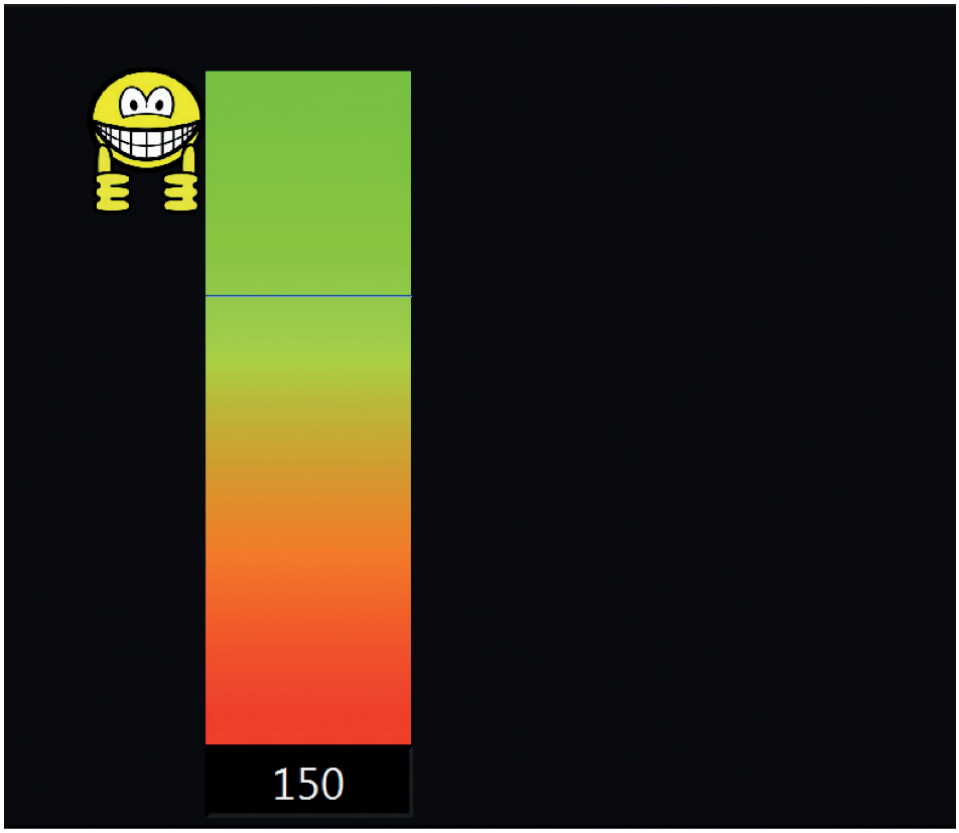


Figure 2. Impression of one of the games used for neurofeedback training using one frequency band. Participants had to try to exceed the bar above the threshold, after which an encouraging smiley popped up on the screen, giving immediate positive reinforcement.

Measures

Electroencephalography. A 5 minute 21-channel EEG resting-state measurement with eyes closed was conducted with Nexus-32 hardware and Biotrace software (MindMedia BV). EEG measurements were collected from 19 standard 10/20 positions (Herbert & Jasper, 1958), and the right and left mastoid with a sampling rate of 512 samples per second. The left mastoid served as the online reference. Flat type electrodes were placed above and below the left eye and at the outer canthi of each eye to correct for vertical and horizontal eye movements. EEG magnitude across delta (0.5-3.5 Hz), theta (3.5-7.5 Hz), alpha (7.5-12 Hz), beta (12-20 Hz), SMR (12-15 Hz), high beta (20-32 Hz), and gamma (32-49 Hz) frequency bands was assessed. Magnitude changes in delta, theta SMR and high beta frequency were used for analysis. For analysis, custom-made Matlab scripts (version R2012b) were used. First, data from the resting-state measurements were imported into EEGLAB, bandpass filtered between 1-40 Hz, and inspected for gross movement artifacts which were then manually removed. Subsequently, epochs of 4 s length were created. Epochs containing amplitudes exceeding ±100 μV at any scalp electrode and/or epochs containing abnormally distributed data (i.e., joint probability or kurtosis >5 SD from expected mean values) were rejected. From the remaining epochs, the first 40 were transformed into FieldTrip format (version 20160620). Power values for electrode Cz were computed using a fast Fourier analysis with a Hanning taper as implemented in FieldTrip. Mean power values for delta, theta, SMR and high beta frequency bands were calculated and transferred to SPSS for statistical analysis.

Barratt Impulsivity Scale-11 (BIS-11). The Dutch version of the BIS-11 (Lijfijt & Barratt, 2005) is a 30-item self-report questionnaire which assesses common impulsive behaviors and preferences across three second-order factors: motor, attentional and non-planning. An example of a BIS-11 item is 'I do things without thinking' and items are scored across a four-point Likert scale ranging from 'rarely/never' to 'almost always/ always'. The BIS-11 is an internally consistent measure of impulsivity among inmate populations (Cronbach's α=. 80) (Patton, Stanford, & Barratt, 1995).

Cued Go/No-go task. The cued Go/No-Go task is a continuous performance test designed to measure response inhibition (Fillmore, 2008). The task was programmed in E-Prime (version 2.0.10.353). Participants are instructed to respond as quickly as possible to a green square appearing on a screen ('Go target'), but to inhibit responses to a blue square ('No-Go target'). The test consists of 250 targets with equal numbers of Go and No-Go targets. Each target is preceded by either a Go or a No-Go cue, indicating the likelihood of a Go or No-Go target to appear. The likelihood of a correct target after a cue is manipulated with a 80/20 ratio, with 80% being a correct cue and 20% being an incorrect cue. Cues are presented with four fixed stimulus onset asynchronies (100, 200, 300, and 400 ms). The program displays feedback about the accuracy of the response back to the participant, as well as the time (in milliseconds) it took the patient to respond to the target. Outcome measure is the number of commission errors, reflecting the failure to inhibit a prepotent response to a no-go square. Number of commission errors in a cued Go/No-Go task is a valid measure of impulse control in a substance abusing population (Fillmore, 2003).

Modified version of the Desire for Alcohol Questionnaire Short Form (DAQ-SF)
The short form of the DAQ-SF is a self-report questionnaire which measures levels of craving for alcohol among 14 items scored on a seven-point Likert scale (ranging from 1=strongly disagree to 7= strongly agree). The DAQ-SF has been shown to be a reliable measure to assess craving in a substance-dependent population (Cronbach's α=.70) (Courtney et al., 2013). For the purpose of this study, items from the Dutch version of the questionnaire (Franken et al., 2003) were modified to measure desire for drugs in general, as opposed to being restricted to measure desire for alcohol only. An example of a modified item is 'All my tension would completely disappear if I drank now' into 'All my tension would completely disappear if I used drugs now'. The modification was made due to the fact that alcohol use is very rare in an inpatient setting, whereas use of other drugs (e.g., cannabis or cocaine) is more common.

Drug use. Scores on urine or breathalyzer drug testing were collected for each participant. Drug testing was performed regularly for each patient as part of treatment facility policy. Drug use was operationalized as any positive scoring for use of illegal substances. Illegal substances included all known drugs, as well as alcohol and non-prescribed medication used as recreational drug consumption (e.g., inhaled methylphenidate). According to treatment facility policy, refusal to undergo drug testing was scored as positive drug testing. To score substance abuse, the item 'substance abuse' on the risk assessment scale 'Historische, Klinische, Toekomst- Revised (HKT-R) (Historical, Clinical, Future - Revised) was used (Spreen, Brand, Ter Horst, Bogaerts, 2014; Bogaerts, Spreen, Ter Horst, & Gerlsma, 2017). This item was scored on a five-point scale, indicating number of positive drug testing as well as willingness to undergo drug testing. Scores ranged from 0 - no drug use whatsoever, to 4 -the patient tested positive at least twice and also refused to undergo drug testing.

Data and statistical analysis
All participants who completed pre- and post-treatment measures were included in the statistical analysis (*N*=42). For analysis of drug testing, weekly reports of two of the patients from the control group were not available, therefore the analysis of drug testing consists of data from 40 patients.
All data were analyzed with SPSS version 25 (IBM Corp).
Due to violations of statistical assumptions concerning normality and homoscedasticity of almost all dependent variables (BIS motor, BIS attentional, BIS, DAQ-SF, delta magnitude, theta magnitude, SMR magnitude and Cued Go/No-Go commission errors), non-parametric tests were employed. To test for differences between treatment conditions pre-treatment, Mann-Whitney U tests were performed for pre-treatment scores on BIS-11 total score, BIS-11 subscales 'motor', 'non-planning', and 'attentional', as well as scores on DAQ-SF, number of commission errors, drug testing and mean theta and SMR magnitude. A Wilcoxon signed-ranks test was performed to assess changes within groups between pre- and post-treatment for all dependent variables.
A repeated-measures ANOVA with Time as within-subject variable and Treatment condition as a between-subject variable was performed. To assess significance, a within-groups effect size was used (Eta squared). Cut-off scores were used according to Cohens rules in order to assess whether effect size were small=0.02, medium=0.13 or large=0.26 (Cohen, 1988).

Pearson's correlations were performed to test for relations between changes in delta, SMR, high beta and theta frequency magnitude pre- versus post-treatment and all behavioral measures. Only results significant at the .05 level will be reported.

Results

Patient flow

Of those assessed (N=258), 47.3% of patients (*n*=136) were excluded due to not fitting the inclusion criteria. 52.7% (*n*=122) of patients were eligible for participation. Those eligible were randomly assigned to either the neurofeedback training + TAU group (N=42) or TAU only group (N=41). Figure 1 summarizes the flow of participants throughout the study.

42 patients completed all post-treatment measurements, of which 21 patients participated in the TAU only group and 21 patients in the neurofeedback training + TAU group. None of the patients in the neurofeedback training + TAU group was able to complete training within the scheduled 10 weeks. This was due to holidays and planning issues, but also because some patients were mentally unable to complete a training session, or caused aggressive incidents which resulted in temporary separation/placement on a specialized crisis unit. It sometimes also happened that patients were unmotivated to attend a training session. Participation in the study therefore lasted for an average of 14.1 (*SD*=5.32) weeks per patient.

When pre-treatment measurements were assessed, mean number of months in treatment was 93.6

Table 1. Baseline sample characteristics (N=42)

	Neurofeedback training group	**TAU only group**
Mean age in years (range)	38.00 (21-55)	38.57 (26-55)
Mean number of months in treatment at T0 (range)	91.90 (19-248)	95.30 (10-290)
Mean number of Axis I and II diagnoses (range)	4.5 (2-8)	4.6 (1-7)
Mean PCL-R score	23.86 (15-32)	23.77 (15-36)

Table 2. Type of substance use diagnosis for the neurofeedback training group and the TAU only group (N=42)

Type of substance use diagnosis	**Neurofeedback training group**	**TAU only group**
Alcohol	9	13
Cannabis	12	19
Amphetamines	4	8
Opioids	1	4
Cocaine	5	9
Sedative	2	1
Other	3	0

months (*SD*=67.18). The large standard deviation was caused by five patients who had already been hospitalized for more than 200 months in the treatment facility. Participants did not differ with regard to mean age between the neurofeedback training + TAU group (M=38.00, *SD*=9.18) and TAU only group (*M*=38.57, *SD*=8.41) (t(40)=-.22, *p*=.63), or mean number of Axis I and II DSM-IV-TR diagnoses (neurofeedback training group *M*=4.52, *SD*=1.47; TAU only group *M*=4.57, *SD*=1.63, t(40)=-.09, *p*=.38), or month in treatment prior to inclusion (neurofeedback training group *M*=91.90, *SD*=61.70; TAU only group *M*=95.30, *SD*=73.76, t(40)=-.16, *p*=.87). See Table 1, 2 and 3 for sample characteristics.

Table 3. Comorbid Axis I and II diagnosis and index offense for the neurofeedback training group and the TAU only group (N=42)

Comorbid Axis I disorder	**Neurofeedback training group**	**TAU only group**
Pervasive Developmental Disorder	2	0
ADHD	6	3
Disorders in the schizophrenia spectrum	12	10
Mood and anxiety disorder	2	2
Pedophilia	1	1
PTSD	2	3
Comorbid Axis II disorder		
Antisocial personality disorder	8	7
Borderline personality disorder	2	4
Personality disorder not otherwise specified	7	7
Avoidant personality disorder	1	1
Index offense*3		
Homicide	9	7
Sexual offence	2	4
Arson	1	2
Violence	3	3
Threat against life	4	3
Theft	2	2

**1 Pervasive developmental disorder: Autism spectrum disorder, Asperger disorder, developmental disorder not otherwise specified*
**2 ADHD: All types of attention-deficit disorder*
**3 Index offense: In case of more than one index offense, the most serious one is reported, based on the classification given in Nieuwenhuizen et al. (2011).*

Baseline differences between groups

A Mann-Whitney U test indicated that scores on SMR magnitude on pre-treatment measurements were significantly higher for patients in the neurofeedback training group (*Mdn*=1.00) than for patients in the TAU group (*Mdn*=.58), *U*=131.00, *p*=.02, *r*=.35.

Differences within groups

Only the neurofeedback training group showed significant effects between pre- and post-treatment scores. Within-groups differences on the BIS-11 subscale 'motor' (pre-treatment: *Mdn*=23.00) showed a significant decrease post-treatment for patients in the neurofeedback training group (*Mdn*=21.00), *Z*=2.076, *p*=.04, *r*=.45, as well as a significant decrease in craving scores post-treatment (*Mdn*=34.00) as measured with the DAQ-SF, *Z*=2.091, *p*=.04, *r*=.46. SMR mean amplitude also significantly increased from pre-treatment (*Mdn*=1.00) to post-treatment (*Mdn*=1.22), *Z*=2.068, *p*=.04, *r*=.45.

Table 4. Main outcome measures of repeated measures analysis (N= 42).

	Neurofeedback training		**TAU**		**Post-/Premeasurement**			
	T0	T1	T0	T1	Time	Group	Time x Group	ES
	M (SD)	M (SD)	M (SD)	M (SD)	F *(P)*	F *(P)*	F *(P)*	η^2
BIS-11	67.05 (11.05)	63.10 (10.88)	63.33 (12.23)	62.62 (11.5)	3.02 (.09)	.41 (.52)	1.45 (.24)	.03
BIS-11 motor	24.10 (6.24)	21.67 (3.97)	21.81 (4.49)	20.95 (4.42)	5.61 **(.02)**	1.27 (.27)	1.28 (.26)	.03
BIS-11 nonplanning	25.86 (4.21)	25.05 (.5.82)	25.3 (6.18)	25.6 (6.03)	.14 (.71)	.00 (.99)	.6 (.44)	.02
BIS-11 attentional	17.10 (3.36)	16.38 (3.2)	16.19 (4.06)	16.05 (3.79)	.96 (.33)	.36 (.55)	.43 (.52)	.01
DAQ-SF	44.19 (17.77)	36.38 (20.45)	42.72 (17.48)	39.24 (16.49)	6.23 **(.02)**	.02 (.89)	.92 (.34)	.02
Commission errors	2.05 (3.44)	1.52 (1.91)	1.00 (1.00)	1.14 (1.42)	.3 (.59)	1.59 (.21)	.92 (.34)	.02
Drug use	.53 (.64)	.38 (.50)	.23 (.31)	.22 (.35)	1.67 (.2)	2.91 (.1)	1.27 (.27)	.03
Theta	3.94 (3.67)	4.31 (3.53)	2.54 (1.64)	2.75 (1.72)	1.81 (.19)	3.12 (.09)	.14 (.71)	.00
SMR	1.01 (.52)	1.23 (.66)	.65 (.39)	.64 (.35)	5.00 **(.03)**	10.56 **(.00)**	5.47 **(.02)**	.12

Sample sizes were n=42, except for scores on drug use which was n=40.
Significant results are indicated in bold print.
Pearson's correlations revealed no significant correlations (p>.05) between the difference in SMR or theta magnitude by the end of the training and behavioral outcome measures.

Outcome measures

The main outcome measures are presented in Table 4. On the primary outcome measures, results on the 'motor' subscale of the BIS-11 showed a significant effect for Time ($F(1, 40)=5.61$, $p=.02$), but not for Time x Group ($F(1, 40)=1.28$, $p=.28$). For the drug craving measure DAQ-SF, there was a significant effect for Time ($F(1, 40)=6.23$, $p=.02$), but not for Time x Group ($F(1, 40)=9.2$, $p=.34$). There was a significant Time x Group effect for mean SMR magnitude ($F(1, 40)=5.47$, $p=.02$), indicating an increase for mean SMR magnitude in the neurofeedback training group post-treatment. Results for drug use, mean theta magnitude and number of commission errors post-treatment were not significant.

Pearson's correlations revealed no significant correlations ($p>.05$) between the difference in SMR or theta magnitude by the end of the training and behavioral outcome measures.

Discussion

This RCT was conducted to investigate to what extent a theta/SMR neurofeedback training protocol in combination with TAU is able to reduce impulsivity and symptoms of SUD in a population of male forensic psychiatric patients residing in a FPC. The RCT compared a neurofeedback training group of 21 patients who received neurofeedback training in addition to TAU, to a control group of 21 patients receiving TAU only. Changes in targeted frequency bands and changes in levels of impulsivity, drug craving, and drug intake post-treatment were examined in the neurofeedback training group, and compared to patients in the TAU only group. Results indicate that SMR magnitude showed a significant increase post-treatment in the neurofeedback training group, whereas theta magnitude did not show any changes. Surprisingly, patients in the neurofeedback training group had significantly higher SMR magnitude pre-treatment than patients in the TAU only group.

Levels of drug craving and motor impulsivity as assessed with the BIS-11 decreased equally for patients in the neurofeedback training group and the TAU only group. Therefore, the combination of TAU and neurofeedback training was not more effective than TAU only. Other measures of impulsivity and number of drug use did not change post-treatment.

To the best of our knowledge, this is the first RCT study investigating the effects of neurofeedback training in a population of forensic psychiatric patients. Studies on investigating neurofeedback training have steadily increased in the past two decades, but neurofeedback training is rarely used as a treatment option for forensic psychiatric patients. This could partially be due to the fact that these patients usually present with a variety of disorders, and research on the effects of neurofeedback usually exclude patients with comorbid disorder (e.g., (Janssen et al., 2017; Kropotov, Grin-Yatsenko, Ponomarev, Chutko, Yakovenko, & Nikishena, 2005; Mayer, Wykoff, Schulz, & Strehl, 2012). Furthermore, practitioners might be hesitant to employ a treatment modality for which the efficacy in such a complex patient population has yet to be demonstrated. The fact that effects of neurofeedback training were not superior to TAU only has also been observed in other studies that applied neurofeedback in an attempt to reduce levels of impulsivity. Bink, van Nieuwenhuizen, Popma, Bongers, and van Boxtel (2015) employed a theta/SMR protocol in children with ADHD, but found the combination of TAU and neurofeedback as effective as TAU only. Schönenberg et al. (2017) also found no superiority of a theta/beta

neurofeedback training over a meta-cognitive therapy, or even a sham neurofeedback condition. Both Bink et al. (2015) and Schönenberg et al. (2017) applied the training in subjects with a single, well-defined disorder without any comorbidities. Hence it can be argued that for patients with multiple disorders and characterized by high levels of impulsivity, finding behavioral improvements due to neurofeedback training may be even more difficult.

The results of the current study also raise the question as to how participants failure to decrease theta activity over the course of the training is associated with the lack of behavioral improvements post-treatment. To date, there are no clear guidelines how many neurofeedback training sessions are actually needed to achieve significant treatment effects, it is possible that improvements in the theta frequency band could have been achieved with more sessions. Bink et al. (2015) found that adolescents with ADHD were better able to suppress theta frequency by the end of the training sessions than at the beginning of neurofeedback training. In the study by Bink et al. (2015), 37 sessions were employed, but they still did not observe an effect of the neurofeedback training in the reduction of impulsivity. It may be the case that the 20 sessions of neurofeedback provided in the current study simply were not enough for this patient group to learn to regulate the theta frequency band. However, patients' inability to adhere to the training schedule of two neurofeedback sessions a week might be indicative of the feasibility of a neurofeedback protocol that employs even more sessions. Throughout the current study, it was difficult to keep patients engaged in the study. While the specific patient population at hand is difficult to engage in treatment no matter which treatment is applied, the fact that none of the patients in the neurofeedback training group was able to attend two sessions a week is concerning. This was partially due the fact that neurofeedback software is still in its infancy and options concerning the employed training methods are limited. In most cases, the implemented video games are quite simplistic. A lot of patients reported that they found the intervention dull, which most likely was of negative influence on treatment motivation. An abbreviated protocol might be better suited for this patient population in terms of keeping patients engaged in the training. Also, as results of the current study showed no significant relation between patient's reduction in theta magnitude and behavioral outcome measures, it remains unclear as to whether (more) improvements in theta activity regulation can lead to (better) clinical improvements at the behavioral level. However, patients did manage to increase SMR magnitude post-treatment. It is possible that the SMR frequency band is easier to regulate with neurofeedback training. In a recent study by Fielenbach, Donkers, Spreen & Bogaerts (2018a), that focused on whether forensic psychiatric patients are actually able to learn to regulate cortical activity through neurofeedback training, more patients were able to systematically increase SMR activity as opposed to reducing theta activity. In a study by Doppelmayr, and Weber (2011), healthy participants were better able to regulate SMR activity than to change the theta/beta ratio, and a recent study by Janssen et al. (2017) showed that adolescents were not able to inhibit their theta frequency, but did manage to increase beta activity. It is unclear why patients in the neurofeedback training group showed higher pre-treatment SMR magnitude than patients in the TAU only group, as patients distribution over groups was random. However, previous studies with healthy participants have suggested that pre-treatment SMR magnitude is a predictor of participants ability to increase of SMR magnitude over the course of neurofeedback training (Blankertz et al., 2010; Clarke, Barry, Bond, McCarthy, & Selikowitz, 2002). Possibly, the high(er) pre-treatment levels of SMR magnitude contributed to the finding that patients did manage to increase SMR magnitude over the course of training.

Recently, QEEG-guided neurofeedback protocols are increasingly implemented in clinical practice. With these protocols, pre-treatment EEG-deviations are first assessed and the applied neurofeedback protocol then focusses on treating these EEG-deviations, as opposed to applying a standard neurofeedback protocol to all participants. While there is also discussion in the literature about the use of QEEG approach of neurofeedback treatment (e.g., Johnson, & Bodenhamer-Davis (2009), this approach fits with the rise of personalized medicine in the past decade, where a treatment approach tailored to the individual is applied rather than a one-size-fits all approach. Especially for forensic psychiatric patients, usually presenting with a wide range of comorbidities, manifesting through various deviations in EEG-frequencies, this might be a more suitable approach than applying standardized neurofeedback protocols.

Limitations and recommendations for future studies

Patients taking prescription medication were allowed to keep taking these medications during the course of the study. Given the special setting where this study was conducted, limiting medication intake would have severely hampered patient recruitment. However, almost all types of medication commonly prescribed for forensic psychiatric patients tend to have effects on EEG-frequencies. Several studies have shown that stimulant medication such as methylphenidate normalizes EEG-frequencies and may lead to a reduction of theta band magnitude and an increase in low beta bands magnitude (e.g., (Saletu, Anderer, & Saletu-Zyhlarz, 2006; Johnson & Bodenhamer-Davis, 2009). Medication for disorders in the schizophrenia spectrum such as clozapine has been shown to increase theta activity (Hyun, Baik, & Kang, 2011). It is very well possibly that the results of this study were to some extent influenced by type and/or dosage of patient's medication. A theta/SMR neurofeedback protocol might not lead to significant changes in EEG-frequencies when these frequency bands are already normalized due to use of medication, although this remains speculative. In this study, changes in medication were insufficiently tracked during the course of the study. Future studies should investigate the effects of medication on the EEG spectrum more closely before applying neurofeedback, or should at least control for medication intake during the analysis to achieve more conclusive results. Another limitation concerning medication is the fact that some medication, such as aripiprazole is known to have positive effects on levels of craving (Beresford, Buchanan, Thumm, Emrick, Weitzenkamp, & Ronan, 2017), which could have influenced the results on the craving questionnaire DAQ-SF.

Also, with the patient sample of this study, there was heterogeneity concerning substances used by study participants. This is quite common in patients with SUD, as many patients are polydrug abusers. This may have altered the results, and potentially influence the effects of neurofeedback in these patients. Also, we followed treatment facility policy, where a refusal to undergo drug testing is scored as having a positive drug testing. There is no way to be certain that patients who refused to undergo drug testing did, in fact, use illicit substances. However, given our clinical experience, patients refusal to undergo drug testing usually lies in the fact that they have relapsed in drug use, as patients have no reason to refuse to undergo drug testing other than fear of having drug use exposed. Refusal to undergo drug testing will result in loss of privileges, so that refusing to undergo drug testing comes at a reasonable cost to patients.

Also, the fact that none of the patients in the neurofeedback training group were able to complete the training in the scheduled amount of time could have influenced the results. Possibly, results achieved in terms of enhancing or inhibiting EEG frequencies were lost in between sessions

because patients were not able to follow the scheduled training sessions. To date, there is no conclusive research indicating the ideal number of neurofeedback training sessions or the most beneficial interval time in between training sessions. For the current study, adhering to a very strict training schedule, where patients would have been excluded from further participation whenever they missed a session, would have resulted in a very high number of drop-out and consequently in lower power of the results found. Nonetheless, the failure of patients' adherence to the schedule could have been of influence on the study results.

Another limitation of the current study is that a sham-neurofeedback control group was not added to the study. While some authors challenge the use of a sham neurofeedback condition (e.g., Barth, Mayer, Strehl, Fallgatter, & Ehlis, 2017), as even a sham-based neurofeedback training can lead to treatment outcomes, it could have been useful to add a waiting list group as an untreated control condition.

Future studies should also investigate whether results in terms of patients ability to increase or decrease their frequency magnitude vary when manually adjusted thresholds are applied versus when automatically adjusted thresholds are applied. Manually adjusted thresholds are subject to the expertise of the neurofeedback trainer, and therefore also subject to, for example, inattention of the trainer. Automatically adjusted thresholds provide a more objective way of adjusting thresholds, which might be better suitable for scientific purposes.

Conclusion

The current study highlights that more research is needed to assess the efficacy of a theta/SMR neurofeedback protocol for the reduction of impulsivity, drug craving and drug intake in forensic psychiatric patients with substance abuse problems. Results showed that patients were unable to learn the whole neurofeedback protocol as they didn't succeed in reducing theta activity. Future research should focus on assessing which patients will be able to benefit from neurofeedback training at an early stage of the employed training sessions. Given that neurofeedback training is often times applied in vulnerable patient populations such as children, adolescents and patients with severe mental illness or addiction, it can be considered unethical to enroll these patients in any treatment with the knowledge that it will most likely not lead to beneficial outcomes in terms of reduction of clinical symptoms. Weber, Köberl, Frank, and Doppelmayr (2011) have made an important start with their research on predicting successful learning of SMR neurofeedback in healthy participants. This research needs to be extended to clinical populations.

Chapter 6

Theta/SMR neurofeedback training works well for some forensic psychiatric patients, but not for others: a sham-controlled clinical case series

Under review at International Journal of Offender Therapy and Comparative Criminology

Abstract

EEG-neurofeedback could be a promising treatment for forensic psychiatric patients. Increasing evidence shows some patients are unable to regulate cortical activity. Before neurofeedback can be applied successfully, research is needed to investigate the interpersonal mechanisms responsible for patients ability to respond to neurofeedback. A single-case experimental design allows for close monitoring of individual patients, providing valuable information about patients' response to the intervention and the timeframe in which changes in clinical symptoms can be observed. Four patients with DSM-IV-TR substance use disorder and various comorbidities participated in a sham-controlled clinical-case study. Self-report level of impulsivity and craving were assessed. Results indicate that one patient benefitted significantly more from neurofeedback than the others. This patient reported less impulsivity and reduced levels of self-reported craving. The findings suggest that there may be great interindividual differences in patient's ability to regulate cortical activity, as well as in the effectiveness in reducing clinical symptoms.

Introduction

Forensic patients are characterized by the presence of diverse and complex problems, such as persistent and co-morbid psychiatric disorders (Palijan, Radeljak, Kovac, & Kovacevic, 2010), serious criminal offenses and cognitive disorders. Their treatment motivation and readiness is often low, there is often times a lack of problem insight, and treatment compliance is problematic. A complicating factor for effective treatment and compliance is the presence of complex comorbid problems such as high levels of impulsivity and substance use disorder (SUD) (Schuringa, Heininga, Spreen, & Bogaerts, 2016). As a consequence, these individuals are more likely to reoffend (Palmer & Humphries, 2016). Following Gottfredson and Hirschi's general theory of crime (1990), in which they state that low self-control and high impulsivity significantly predict recidivism, effective treatment of impulsivity is needed.

Studies have shown that changes in electroencephalographic (EEG-)frequencies after neurofeedback training can positively influence motor control and cortical inhibition function (Sokhadze, Stewart, Tasman, Daniels, & Trudeau, 2011). EEG-based neurofeedback training could therefore be a promising treatment method for forensic psychiatric patients. It is increasingly used in the treatment of various psychiatric disorders (for review see Fielenbach, Donkers, Spreen, Visser, & Bogaerts, 2018b). Training protocols where the sensorimotor rhythm (SMR, 12-15 Hz) frequency is enhanced, while inhibiting slower brain waves such as theta (3.5-7.5 Hz) have shown promising results in the reduction of high levels of impulsivity commonly found in patients with ADHD (e.g., Fuchs, Birbaumer, Lutzenberger, Gruzelier, & Kaiser, 2003). Neurofeedback training uses real-time display of brain activity and aims at normalizing EEG-frequencies that have shown to be deviant in various disorders and that are thought to underlie the manifestation of clinical symptoms by means of operant conditioning.

The effectiveness of this type of training can be assessed in two complementary ways: 1. Through changes in cortical activity post-training, i.e., normalization of deviant brain wave patterns, or increase/decrease of EEG-activity in particular frequency bands, and 2. through improvements at the behavioral level underlying specific clinical symptoms (e.g., the ability to inhibit prepotent actions in favor of more suitable behavior) (Rogala, Jurewicz, Paluch, Kublik, Cetnarski, & Wrobel, 2016).

There is increasing evidence that not all patients benefit from neurofeedback training, as they seem unable to learn to regulate cortical activity through neurofeedback within the number of sessions provided (e.g., Zuberer, Brandeis, & Drechsler, 2015). These patients do not show the assumed effects within the trained frequency bands, with as many as 25% of participants being categorized as so-called 'non-responders' (Enriquez-Geppert et al., 2013; Zoefel, Huster, & Herrman, 2011). Other studies show that patients do achieve regulation of deviant brain frequencies, but without showing improvements in clinical symptoms post-training (Fielenbach et al., 2018a). It can be argued that successful regulation of brain activity is a necessary condition for achieving behavioral symptom improvement.

However, there are only a limited number of studies that report how many patients achieved successful regulation of cortical activity, and that also link successful regulation to behavioral outcomes. Also, most studies use randomized controlled trials (RCTs) designs, in which one group receiving the training is compared to another receiving treatment as usual (TAU), which does not reveal individual differences which might exist between patients (Alkoby, Abu-Rmileh,

Shriki, & Todder, 2017). Before neurofeedback can be applied successfully in populations with vulnerable patients, additional research is needed to investigate these interpersonal mechanisms between participants, which are (at least partially) responsible for a patients ability to respond to neurofeedback training.

Clinical case studies involve an experimental design of a specific person, group or event. This designs offers the possibility to investigate the effect of a treatment over time. It allows for close monitoring of an individual patient, providing valuable information about a patients' response to the intervention and the timeframe in which changes in clinical symptoms can be observed (Van Yperen, Veerman, & Bijl, 2017). It has also been shown that a series of well-conducted clinical case studies can provide the same level of experimental rigor and high level of internal validity as an RCT (Byiers, & Reichle, & Symons, 2012; Rizvi & Nock, 2008; Task Force APA; 1995). It will provide practitioners with detailed information about treatment effects in the current environmental setting, thereby reducing the gap between research and practice (Morgan & Morgan, 2001), providing valuable insights for further research.

The current study will apply a restricted sham-controlled series of clinical-case studies in male forensic psychiatric patients. Two single-case experimental designs will employ a SMR neurofeedback protocol, where the SMR-frequency (12-15 Hz) is enhanced and the theta frequency (3.5-7.5 Hz) is inhibited, while two other clinical case studies will employ a sham neurofeedback protocol. In substance abuse, individuals present with elevated scores on impulsivity measures, independent of type of specific addiction (Nielsen et al., 2012; Fillmore & Rush, 2006). Drug intake can be seen as loss of control over a patients' restriction from using. Especially for forensic psychiatric patients who present with SUD and various other comorbidities that are typically found in this patient population, it can be argued that impulsivity is especially pronounced. Higher levels of impulsivity have also shown to affect severity of symptoms of substance dependency, in that patients high in impulsivity report higher levels of drug craving (Tziortzis, Mahoney, Kalechstein, Newton, De la Garza, 2011; Bornovalova, Levy, Gratz, & Lejuez, 2010). Therefore, the current study will apply a SMR neurofeedback training protocol aimed at the reduction of self-reported levels of impulsivity. Between-session effects of mean SMR and theta magnitude will be monitored. Throughout the course of the study self-report measures of impulsivity (the Barratt Impulsivity Scale-11 (BIS-11) 11 (Patton, Stanford, & Barratt, 1995) and craving will be monitored frequently (a modified version of the Desire for Alcohol questionnaire DAQ-SF) (Franken, Rosso, & Honk, 2003).

Method

Design

A single-subject ABA-design is employed (Rizvi & Nock, 2008). With this single-case experimental design, a no-training baseline phase (A^1) is followed by a neurofeedback training phase (B), which is then followed again by a no-training follow-up phase (A^2). In phase B, participants receive eight sessions of theta/SMR neurofeedback training during 10 weeks (Figure 1). Throughout the course of the study, self-report measures of impulsivity and levels of craving of the participating subjects are repeatedly measured two times a week. In the no-training phases A^1 and A^2, participants follow TAU only. TAU is different for every participant, as the different treatment modalities dependent

on the specific diagnosis and behavioral complaints of each patient.
Participants are randomly assigned to either real or sham-neurofeedback training. The study is single-blind, with participants not knowing which type of feedback they are receiving. We hypothesized that after eight neurofeedback sessions, patients receiving real neurofeedback training should show: a) evidence of being able to regulate cortical activity by enhancing SMR-frequency and reducing theta-frequency, and b) at least a trend towards behavioral improvement through reductions in BIS-11 and/or DAQ-SF scores. Figure 1 shows a graphic display of the study design. In this study, patients who receive the shame training will not benefit from the training.

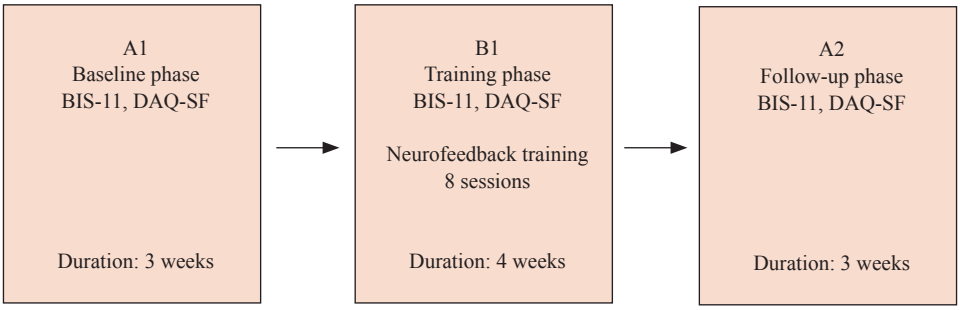


Figure 1: Flowchart of the study design.

Participants

Participants in the current study were male forensic psychiatric patients residing in the Forensic Psychiatric Centre (FPC) Dr. S. van Mesdag, situated in the Netherlands. They all had at least one DSM-IV-TR diagnosis of SUD and a minimum of one comorbid axis I or II disorder, such as schizophrenia or personality disorder (American Psychiatric Association, 2000). They were receiving compulsory treatment by order of the state, after committing a violent crime with a minimum penalty of at least four years according to Dutch jurisdiction (called Terbeschikkingstelling, or TBS; Van Marle, 2002). Due to mental illness, these patients were held only partially responsible for the crime they committed. The patients participating in the current study were selected from the control group of an ongoing RCT, investigating the effects of neurofeedback on impulsivity, craving and substance use (Fielenbach, Donkers, Spreen, & Bogaerts, 2017). Participants in the control group of this RCT received TAU only, without previous neurofeedback training, but participated in assessing self-report scores of impulsivity (BIS-11) and craving (DAQ-SF). The patients for the current study were selected based on their high scores on the BIS-11 and the DAQ-SF. Patients received information about the study and gave informed consent.
The study was conducted according to the principles of the Declaration of Helsinki (version 59, Seoul, October 2008), and in accordance with the Medical Research Involving Human Subjects Act. It has been approved by the Medical Ethical Council of Brabant, the Netherlands (study number NL46390.008.13).

Measures

Barratt Impulsiveness Scale (BIS-11). The BIS-11 (Patton, Stanford, & Barratt, 1995) is a self-report questionnaire measuring the behavioral and personality construct of impulsivity. It consists of 30 items scored on a four-point Likert scale ranging from 1 (rarely/never) to 4 (almost always/always). The total score can be subdivided in three second-order factors: motor, attentional, and non-planning. The BIS-11 has been shown to be an internally consistent measure of impulsivity among inmate populations (Cronbach's α=.80) (Patton, Stanford, & Barratt, 1995). The Dutch version of the BIS-11 was used (Lijffijt, & Barratt, 2005).

Modified Desire for Alcohol Questionnaire - Short Form (DAQ-SF). The DAQ-SF is a self-report questionnaire measuring desire for alcohol at the moment of assessment. It consists of 14 items scored on a seven-point Likert scale, ranging from 1 (strongly disagree) to 7 (strongly agree). The DAQ-SF has shown to be a reliable measure to assess craving in a substance-dependent population (Cronbach's α=.70) (Courtney et al., 2013). For the purpose of this study the word "alcohol" was replaced by the word "drugs" for all questions. Participants were instructed to assess the level of craving at the moment of measurement for drugs in general, with an extra instruction indicating that drugs can range from alcohol to soft- and hard drugs with examples provided. The Dutch version of the questionnaire was used (Franken, Rosso, & Honk, 2003).

Intervention: Neurofeedback

Neurofeedback was applied as implemented in the BrainMarker software engine (BrainMarker Device, BrainMarker B.V. Gulpen). For both training protocols (sham or real), training was performed on the EEG signal recorded from electrode position Cz against a right ear mastoid reference. EEG magnitude was measured across delta (0.5-3.5 Hz), theta (3.5-7.5 Hz), alpha (7.5-12 Hz), beta (12-20 Hz), SMR (12-15 Hz), high beta (20-32 Hz), and gamma (32-49 Hz) frequency bands. For real-neurofeedback, a SMR-enhancement protocol was used, where SMR (12-15 Hz) was enhanced and theta (3.5-7.5 Hz) was inhibited. For sham-neurofeedback, higher beta bands were randomly selected for training (20-23 Hz, 23-26 Hz, 26-29 Hz, and 29-32 Hz). No specific higher beta frequency band was trained systematically. During neurofeedback training sessions, participants learned to control simple video-games by systematically increasing or inhibiting the targeted EEG-frequencies in the desired direction. Patients received positive feedback once a frequency band was maintained above or below a set threshold for 80% of the time. Whenever a patient seemed to be able to successfully control EEG-activity, the feedback threshold was adjusted manually to a more difficult level. During training, participants were consistently encouraged to engage in the training and to not only stare at the screen.

Statistical analysis

Non-overlap of all pairs. For single-case studies, non-overlap of all pairs-scores (NAP-scores) are proposed by some authors as a standard for evaluating single-subject progress (Horner, Carr, Halle, McGee, Odom, & Wolery, 2005). The NAP indicates data overlap between training and no-training phases in single-case studies, and is seen as one of the best indexes to provide insight into the effect of intervention (Parker & Vannest, 2009). NAP-scores are calculated through

pairing every data point between two predetermined phases (e.g., between data from a no-training phase A and data from a training phase B). The NAP-score is determined as the proportion of all pairs for which the baseline score is different from the intervention score in the hypothesized non-overlapping direction (Van Yperen, Veerman, & Bijl, 2017). A NAP-score can range from 0 to 1, with .50 indicating chance level. Parker and Vannest (2009) propose calculating effect sizes for NAP-scores, with NAP-scores from 0.00-.65 indicating weak effects, .66-.92 indicating medium effects and .93-1.0 indicating large or strong effects. For a more detailed description regarding calculating NAP-scores see Parker and Vannest (2009).
NAP scores were used to analyze changes in BIS-11, DAQ-SF, and mean magnitude of theta and SMR frequency bands. A McNemar change chi-square test was performed to assess significance of the NAP-scores. All data were analyzed with SPSS version 22 (IBM Corp).

Simulation Modeling Analysis. A statistical approach that takes autocorrelation into account is Simulation Modeling Analysis (SMA) (Borckardt, Nash, Murphy, Moore, & O'Neil, 2008). SMA can test changes in level and slope factor of an outcome measure between two phases (Van Yperen, Veerman, & Bijl, 2017). The slope is correlated with five possible models of trend, indicating the goodness of fit of the different models. Model 1 indicates a decrease in outcome measure during phase one, which is then followed by an increase during phase two; model 2 indicates a stable phase one, with a decrease during the second phase; model 3 describes a decrease during phase one and subsequently a stable phase two; model 4 indicates a decrease during phase one, which continues during phase two; and model 5 describes a decrease during phase one, and a subsequent stable but then decreasing phase two. SMA-scores were analyzed with the software package 'SMA - Time series analysis program for short time series data streams' (Borckardt, 2006).

BIS-11 and DAQ-SF. To assess changes in scores on BIS-11 and DAQ-SF for each participant, data from the no-training phase was compared to data from the training phase. Specifically, to test for significant differences on outcome measures pre- versus post-training, data from the baseline phase A^1 was paired with data from the follow-up phase $A^{2.}$. It was expected that scores on self-report questionnaires in follow-up phase A^2 would be significantly lower than in baseline phase A^1 for the two patients that received evidence-based neurofeedback training, but not for the two patients that received sham-neurofeedback. To test for changes between no-training and training, data from no-training phases A^1 and A^2 were compared to data from training phase B^1.
First, NAP-scores for all comparisons were calculated for each participant. Next, SMA-scores were analyzed.

Change in frequency bands. Standardized values for each session of neurofeedback were calculated for theta and SMR magnitude. Training rounds in which the frequency magnitude differed more than two standard deviations from the mean were excluded, as these rounds were most likely influenced by artifacts (e.g., due to eye blinks and/or movement). Subsequently, NAP-scores were calculated, comparing the mean amplitude of theta and SMR frequency during the first four sessions of neurofeedback with the mean amplitude of theta and SMR frequency during the last four sessions of neurofeedback.

Results

Three out of four patients completed phase A^1, B^1 and A^2. A fourth patient resigned from participation in the study during phase A^1. Data from this patient was not included in the analysis. Patient characteristics can be found in Table 1.

Table 1. Patient characteristics.

Patient	Age	Axis I	Axis II diagnoses diagnoses	IQ (range)	Type of substance use	Type of NFB
1	30	PTSD[1]	Borderline PD[2] Antisocial PD Histrionic PD	70-80	Cannabis	Real
2	29	-	Antisocial PD	74-83	Cannabis Alcohol	Real
3	43	Schizophrenia (paranoid subtype) Exhibitionism	Antisocial PD	60-70	Stimulants Amphetamines Methylphenidate, Cannabis Alcohol	Sham
4	32	-	Antisocial PD Narcissistic PD Mental retardation	Mental retardation, (precise IQ-score unknown)	Cannabis Amphetamines Alcohol Cocaine	Sham

[1]*Posttraumatic stress disorder*
[2] *Personality disorder*

None of the patients was able to follow neurofeedback training as originally scheduled (two times a week). Due to scheduling issues, lack of motivation, and/or temporary declines in psychological well-being, phase B^1 took slightly longer than the scheduled four weeks for all patients (mean duration 5.4 weeks). When patients didn't attend neurofeedback training during this phase, the questionnaires were still administered. See Table 2 for study flow.

Patient 1 (real neurofeedback training)
Patient 1 showed a significant decrease of BIS-11 scores over the course of the study. When comparing pre- and post-training phases (baseline phase A^1 versus follow-up phase A^2), he showed a significant decrease in BIS-11 total score, with NAP-scores showing a strong effect (NAP=1.00, $p \leq 0.001$). When correcting for autocorrelation of NAP-scores, SMA-analysis revealed a significant level change (r=-.85, $p \leq .05$). The decrease in BIS-11 scores correlated significantly with model 4 of SMA (r=-.86, $p \leq .05$), indicating a decrease in BIS-11 scores that was already present during baseline phase A^1 and that continued during the intervention phase B and follow-up phase A^2. Reduction in BIS-11 scores were not only observable in the total score of the BIS-11, but also in the subscales 'motor' and 'non-planning'. When comparing baseline phase A^1 with follow-up phase A^2, the decrease fit best with model 3 of SMA (r=-.703, $p \leq .05$),

Table 2. Overview of study flow.

Patient	Number of assessments A1	Number of assessments B1/ Number of NFB sessions	Number of assessments A2
1	**6**	**11/8**	**6**
2	**6**	**10/8**	**6**
3	**6**	**9/8**	**6**
4	**6**	**-**	**-**

Patient 1 (real neurofeedback training)

indicating a decrease in outcome measure during baseline phase A1, followed by an increase during follow-up phase A^2. Results regarding the DAQ-SF showed that patient 1 had a significant reduction in DAQ-SF scores when comparing baseline phase A^1 with follow-up phase A^2 (NAP=1.00, $p \leq 0.001$). This effect was still highly significant when correcting for autocorrelation with SMA (level change r=-.96, $p \leq 0.001$). The decrease in DAQ-SF scores fitted best with model 1 (r=-.91, $p \leq .05$), indicating an increase during baseline phase A^1 followed by a decrease in follow-up phase A^2. See Tables 2, 3 and 4 for results and Figures 2 and 3 for a graphical display of BIS-11 and DAQ-SF scores. Patient 1 showed a significant increase in mean SMR magnitude when comparing the first four training sessions to the last four training sessions (NAP=.75; $p \leq .05$), however, this effect did not remain significant when controlling for autocorrelation with SMA (r=.53, $p \geq .05$). Changes correlated by trend with model 2 (p=.07), indicating a stable number of first sessions and an increase during the later sessions. Theta magnitude did not change significantly (NAP=.38, $p \geq .05$) . See Table 2-5 for results.

Patient 2 (real neurofeedback training)

Patient 2 showed a significant reduction in BIS-11 total score when comparing baseline phase A^1 versus follow-up phase A^2 (NAP=.82, $p \leq .001$), however, this effect did not remain significant when controlling for autocorrelation with SMA (r=-.59, $p \geq .05$). The decrease in BIS-11 scores did not significantly correlate with any of the SMA models. Reduction in BIS-11 scores were not only observable in the total score of the BIS-11, but also in all subscales when analyzed with NAP-scores, however these results didn't remain significant when controlling for autocorrelation with SMA. Results regarding the DAQ-SF, showed that patient 2 had a significant slope change (r=-.67, $p \leq .05$) that fitted best with SMA model 1, indicating an increase during baseline phase A^1, followed by a decrease in follow-up phase A^2. See Tables 2, 3 and 4 for results . SMR magnitude showed a decrease between the first four sessions and the last four sessions (NAP=.19, $p \leq 0.01$), but this effect did not remain significant when controlling for autocorrelation with SMA. Changes in theta magnitude were not significant (NAP=.50, $p \geq .05$). See Table 2-5 for results.

Patient 3 (sham neurofeedback training)

Patient 3 showed a significant increase in BIS-11 total score by the end of follow-up phase A^2 (NAP=.22, $p<.001$), although this effect did not remain significant when controlling for autocorrelation with SMA. DAQ-SF scored remained unchanged (A^1 versus A^2: NAP=.50, $p \geq .05$; A^1 versus B: NAP=.64, $p \geq .05$; B versus A^2: NAP=.60, $p \geq .05$). See Table2-5 for results. SMR magnitude showed a significant decrease by the end of follow-up phase A^2 (NAP=.25, $p<.05$),

but this effect did not remain significant when controlling for autocorrelation with SMA. Theta magnitude increased significantly (NAP=.81, $p<0.01$). See Table 2-5 for results and Figures 2 and 3 for a graphical display of BIS-11 and DAQ-SF scores.

Table 3. SMA-scores for comparison between baseline phase A^1 and follow-up phase A^2.

				SMA				
	Instrument	**NAP**	**Level change**	**Model 1**	**Model 2**	**Model 3**	**Model 4**	**Model 5**
	BIS-11							
Patient 1		1.00***	-.85*	-.14	-.74	-.86*	-.86*	-.24
Patient 2		.82***	-.59	.14	-.47	-.36	-.43	.17
Patient 3		.22***	.53	-.37	.73	.43	.64	.36
	DAQ-SF							
Patient 1		1.00***	-.96**	.16	-.91*	-.78	-.91*	-.15
Patient 2		.42	-.01	-.67*	.12	-.42	-.18	-.35
Patient 3		.50	-.28	-.2	-.09	-.25	-.17	.15

p≤0.05=; p≤0.01=**;p≤0.001=****

Table 4. SMA-scores for comparison between baseline phase A^1 and training phase B.

				SMA				
	Instrument	**NAP**	**Level change**	**Model 1**	**Model 2**	**Model 3**	**Model 4**	**Model 5**
	BIS-11							
Patient 1		.79***	-.44	.26	-.5	-.58*	-.58*	-.52
Patient 2		.58	-.04	-.21	.18	.03	.16	.31
Patient 3		.42***	.35	.13	.09	.29	.16	-.14
	DAQ-SF							
Patient 1		.47	-.17	.5	-.45	-.13	-.39	-.48
Patient 2		.79***	-.47	-.05	-.38	-.74*	-.56*	-.45
Patient 3		.64	-.22	.21	-.29	-.2	-.28	-.25

p<0.05=; p<0.01=**; p<0.001=****

Table 5. NAP and SMA-scores for comparison between training phase B and follow-up phase A^2.

				SMA				
	Instrument	**NAP**	**Level change**	**Model 1**	**Model 2**	**Model 3**	**Model 4**	**Model 5**
	BIS-11							
Patient 1		.95***	-.72*	-.43	-.66*	-.67*	-.71*	.10
Patient 2		.79***	-.34	.16	-.29	-.04	-.12	.41
Patient 3		.49	.19	-.37	.41	-.02	.16	-.07
	DAQ-SF							
Patient 1		.98***	-.91***	-.44	-.88*	-.79	-.88*	.15
Patient 2		.18***	.76*	.1	.84*	.55	.7	-.2
Patient 3		.60	-.09	-.23	.03	-.15	-.09	-.00

p<0.05=; p<0.01=**; p<0.001=****

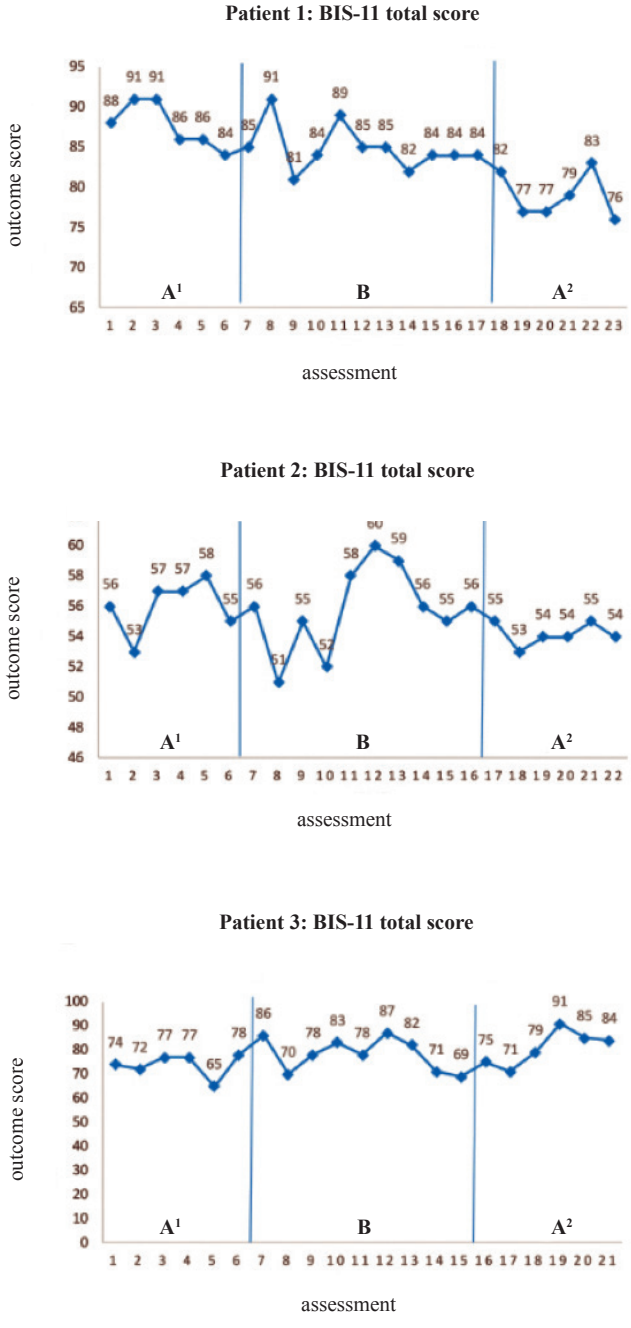
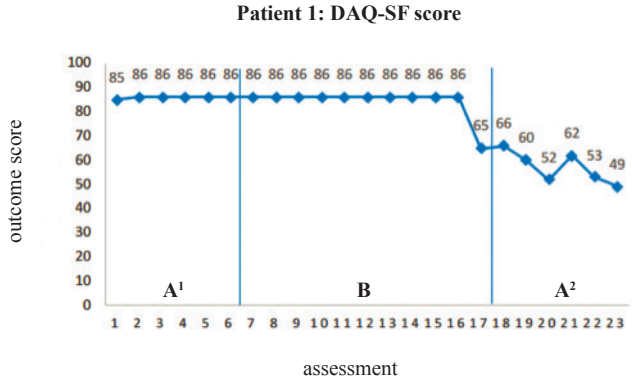
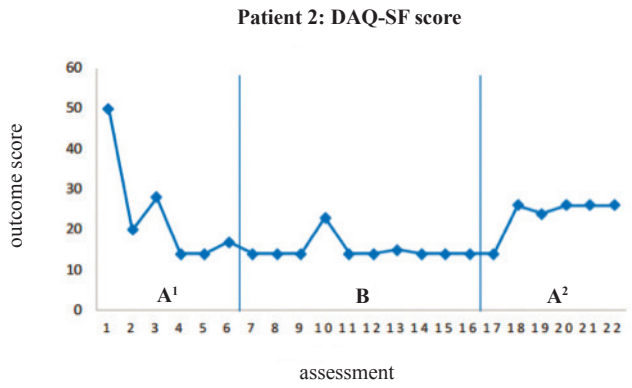


Figure 2: BIS-11 total scores for patient 1, 2 and 3 over all study phases.





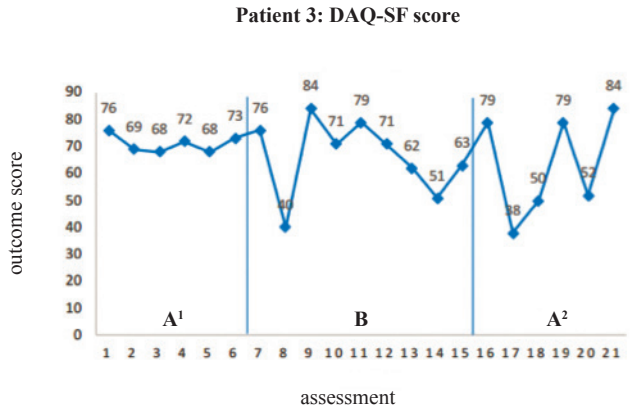


Figure 3: DAQ-SF scores for patient 1, 2 and 3 over all study phases.

Discussion

To the best of our knowledge, this is the first study to employ a sham-controlled clinical case experimental study among forensic psychiatric patients, investigating the efficacy of theta/SMR neurofeedback training in reducing levels of impulsivity and craving. Four patients were randomly assigned to either eight sessions of theta/SMR or eight sessions of sham-neurofeedback training. During the course of the study, patients self-report level of impulsivity with the BIS-11 and self-report levels of craving with a modified version of the DAQ-SF were assessed.

One of the patients benefitted significantly more from neurofeedback training than the others. This patient reported significantly less impulsivity as measured with the BIS-11, as well as reduced levels of self-reported craving over time. The patient showed a decrease in impulsivity measures that was already observable during the baseline phase, and that was continued during and after the intervention. It is not clear what happened during the baseline phase that set reduction in levels of impulsivity in motion already at this phase. It is possible, though speculative, that since the patient was aware of the fact that his impulsivity measures would be monitored during the course of the study, he was more aware and reflective of his actions, which led to a decrease in impulsivity scores. However, this patient was also the patient with the most severe diagnoses concerning cluster B personality disorders, with a diagnosis of borderline, antisocial and histrionic personality disorder. This patient showed the highest impulsivity scores at the start of the study compared to the other two patients. Despite this, he was apparently better able to reduce impulsivity over the course of training.

Only patient 1 was able to (at least partially) increase his SMR magnitude, although this was no longer significant when controlling for autocorrelation. He showed different patterns of change in EEG magnitude for SMR and theta frequency. For SMR, changes correlated by trend with model 2, indicating a stable number of first sessions and an increase during the last four sessions. As this was only significant by trend, it is possible that more neurofeedback training sessions would have led to a stronger increase in SMR magnitude.

Patient 2 did not seem to benefit much from the neurofeedback intervention, although he received real theta/SMR neurofeedback training as opposed to sham-training. It can only be speculated why this patient did not respond as well to the training as patient 1. As there are no clear guidelines about the necessary number of neurofeedback training sessions to achieve significant effects in terms of increase or decrease in magnitude of the targeted frequency bands, it is possible that the employed eight sessions of training were simply not enough to result in a significant decrease of mean SMR and/or theta amplitude. Common neurofeedback protocols range from 12-30 sessions (see for review Fielenbach et al., 2018b), hence a decrease in mean magnitude of the targeted frequency band might take more than 8 sessions to manifest. On the other hand, previous research has shown that performance in early neurofeedback training sessions predicts performance in later training sessions (Weber, Köberl, Frank, & Doppelmayr, 2011). More training sessions may not necessarily result in more clinically relevant results.

Several possible psychological mechanisms that may influence neurofeedback performance have been suggested in the literature. Witte, Kober, Ninaus, Neuper, & Wood (2013) showed that subjects' belief regarding their ability to gain control over technological devices predicted their performance in a SMR neurofeedback training protocol. Subjects' level of locus of control over the neurofeedback device showed a negative correlation with the power of the SMR. Witte et

al. (2013) suggest that subjects who strongly believe in their ability to control a neurofeedback device consume additional cognitive resources. The higher effort may interfere with the state of relaxation necessary to achieve higher SMR power (i.e. SMR increases times of relaxation see Pfurtscheller, Brunner, Schlogl, Lopes da Silva, 2006; Pfurtscheller & Lopes da Silva, 1999). Witte et al. (2013) showed that participants who reported that they did not apply any specific mental strategy to achieve SMR regulation showed better performance during training. It is also suggested that, with SMR neurofeedback training, participants' motivation is related to successful learning response (Nijboer, et al., 2008; Nijboer, Birbaumer, & Kübler, 2010). In this study, motivation for treatment was not assessed, which is a limitation to this study. Motivational (self-report) questionnaires should be assessed in future studies to help gain insight into the role motivation of study participants plays with regard to neurofeedback performance.

Some studies have suggested that a pattern of EEG-learning should be observable over every session of neurofeedback training (Weber et al., 2011). In our study, only patient 1 showed a significant change in EEG magnitude, but this change was not observable over every session, as the change in SMR magnitude correlated only by trend highest with SMA-model 2, indicating a stable number of first sessions and an increase later in the intervention. For theta, the change in mean magnitude indicated a decrease in mean magnitude at the beginning of training, followed by an increase in theta, which then again decreases later on in the intervention. It is possible that for patients with severe mental disorders, the patterns of EEG-learning are not congruent with patterns of learning in healthy subjects.

Although offered, none of the patients were willing to undergo more than the eight training-sessions provided during the first treatment phase. While it is possible that this reflects patients' low motivation for treatment in general, it is also possible that patients experienced insufficient behavioral improvements to be willing to continue further neurofeedback training. Future research on neurofeedback should focus on investigating which patients will benefit from this type of intervention and which will not. Burdening patients with an intervention they are most likely not going to benefit from can be considered unethical.

Limitations

It is possible that differences in the ability to learn successful regulation of cortical brain activity is at least partially influenced by interindividual differences in clinical diagnosis, IQ, type of substance use disorder or other (unknown) factors. In this study, one of the patients who received real neurofeedback training benefited more from the training than the patient who received sham neurofeedback, but this patient also had higher IQ-scores, and a less severe substance use diagnosis than the patient who received sham neurofeedback. Since the current study did not investigate the influence of other external factors on the effectiveness of neurofeedback training, more research is needed to be able to tell which type of patients will most likely benefit from neurofeedback treatment.

The current study did not investigate possible influences of medication use on the trainability of patients. It therefore remains unclear whether some patients showed better results than others due to differences in medication status. Forensic psychiatric patients tend to use various kinds of medication, it is possible that some patients perform better/worse than others in neurofeedback training due to medication that helps/hinders to regulate frequency bands in the desired direction.

Conclusion

The results of our clinical case studies suggest that at least for some forensic psychiatric patients, neurofeedback training may be a viable alternative form of treatment. Despite the fact that it is difficult to extrapolate the results of this study to the larger population, the findings suggest that there may be great interindividual differences in forensic psychiatrics patient's ability to regulate cortical activity through neurofeedback, as well as in the effectiveness of the training in reducing clinical symptoms.

Additional research is needed to identify the most efficient number of training sessions, to examine possible influences of medication on trainability of patients, and to investigate factors that maximize the possible beneficial effects of neurofeedback training for forensic psychiatric patients. As Alkoby et al. (2017) have stated: "Finding possible predictors that are linked to underlying mechanisms of cortical learning will help to identify important factors that should be taken into account to promote neurofeedback efficacy."

Chapter 7

General discussion

The aim of this thesis was to investigate the efficacy of a theta/SMR neurofeedback intervention as an alternative for standard treatment of forensic psychiatric patients who suffer from disorders characterized by heightened levels of impulsivity, as well as comorbid substance use disorder (SUD). High levels of impulsivity as well as SUD can seriously hamper treatment compliance and progress of forensic psychiatric patients, and therefore can function as risk factors for future reoffending (Duke, Smith, Oberleitner, Westphal, & McKee, 2018; Van der Veeken, Lucier, & Bogaerts, 2016). Individuals with substance abuse problems suffer from a loop in which high levels of impulsivity are linked to the development and maintenance of abuse problems (Charney, Zikos, & Gill, 2010; Jentsch et al., 2014), whereas addictive substances themselves tend to increase impulsivity levels due to the detrimental chemical effects of addictive substances on the brain. This can lead to a structural state of disinhibition and loss of self-control over using (Perry & Carroll, 2008). To date, effective treatment of patients with SUD is still challenging, with relapse rates as high as 60% for opioid addicted patients (Gossop, Steward, Browne, & Marsden, 2002). Treatment forms such as cognitive behavioral therapy (CBT) tend to focus on verbal strategies to manifest change, such as promotion of strategies that promote conscious decision making and attention to action (Crews & Boettiger, 2009) making them less accessible to patients who have difficulties expressing thoughts and emotions. Also, effect sizes of CBT strategies tend to be small, and even diminish when investigated over the long term (Longabaugh & Morgenstern, 1999; Magill & Ray, 2009). A lack of alternative therapies may result in insufficient opportunities to change impulsive and addictive behavior, which can significantly increase the chance of reoffending. Thus, there is a strong need to find suitable and efficient treatment methods for forensic psychiatric patients with SUD and high levels of impulsivity, which provide good results in a preferably short amount of time.

To that end, a randomized controlled trial (RCT), as well as four clinical case studies were conducted with the specific goal to investigate the effects of a theta/SMR neurofeedback training on reducing levels of impulsivity and symptoms of SUD. Successful learning of theta/SMR frequency regulation by neurofeedback training was investigated by determining to what extent performance during training sessions could distinguish responders from non-responders in the regulation of EEG rhythms. The thesis focused on two main components for the application of neurofeedback training in forensic psychiatric patients suffering from SUD: 1) Whether these patients were able to learn the regulation of the targeted EEG-activity through the training, and 2) whether altered EEG-activity in the target frequency range lead to a decrease in levels of impulsivity and symptoms of drug addiction.

Main findings

First of all, a systematic review was conducted of studies that applied neurofeedback training in adult patient populations presenting with disorders commonly found in forensic psychiatric patients. Only studies reporting changes in EEG-frequencies post-treatment (increase/decrease/no change in EEG amplitude/power) were included in the review **(chapter 2)**. Although the search was conducted for numerous disorders, as well as for behavior commonly associated with high levels of impulsivity, the search resulted in only 10 studies that fulfilled the inclusion criteria. The included studies were all related to neurofeedback training in patients with ADHD, schizophrenia, SUD and psychopathy. No studies could be identified that applied neurofeedback for cluster B personality disorders, or impulsive behavior often found in forensic psychiatric

patients, such as violence.

For the studies included, EEG-training protocols as well as number of training sessions varied greatly. Number of applied training sessions ranged from 10 to 33 sessions. Also, results on patients' ability for EEG-learning varied greatly between studies and patient populations. Changes in behavioral outcome measures post-training ranged from no improvements to significant symptom reduction. Uncontrolled studies (Arns, Drinkenburg, & Kenemans, 2012; Mayer, Wyckoff, Schulz, & Strehl, 2012) found improvements in impulsivity, but no superiority of neurofeedback training to TAU could be observed when a sham controlled, blinded approach was employed (Schönenberg et al., 2017). The included studies also investigated neurofeedback training applied in a single, well-defined disorder, with comorbidities usually being a reason to exclude patients from participation. Based on these findings, it can be concluded that more research is needed to be able to make inferences about which protocol or how many training sessions should result in the most beneficial effects for forensic psychiatric patients.

In **chapter 3**, we presented the study protocol for the RCT, as well as for the n-of-1 clinical case series. The study took place in the FPC Dr. S. van Mesdag, a maximum security treatment facility in Groningen, The Netherlands. Patients in this treatment facility have committed a serious crime with a minimal sentence of four years according to Dutch Criminal Law. These patients could not be held fully responsible for the crimes they committed due to serious mental disorders. All patients in the current study had at least one diagnosis of SUD, as well as comorbid Axis I and/or II disorders according to DSM-IV-TR (American Psychiatric Association, 2000). For both the RCT and the clinical case series, primary outcome variables were the degree of impulsivity, as well as levels of craving, and changes in resting-state EEG pattern. First, the RCT design was described, which sought to investigate the effects of 20 sessions of theta/SMR neurofeedback training and compare the results to a control group who received TAU. In this RCT, impulsivity was assessed through a cued Go/No-Go task. Furthermore, actual drug use throughout the study was investigated by collecting results on urine and/or breathalyzer analysis. A power analysis calculation based on a 1-tailed alpha value of .05, a power value of .80 and an effect size of .80 resulted in a recommended sample size of 21 participants in each group. Next, the design for a n-of-1 clinical case study was presented. In the clinical case series, four patients in the control group of the RCT were randomly assigned to either eight sessions of real theta/SMR neurofeedback training or sham neurofeedback training. Comparing the effects of real theta/SMR neurofeedback training to sham neurofeedback training allows for investigating possible placebo effects of this intervention. An ABA design was employed, where a no-training baseline phase (A^1) was followed by a neurofeedback training phase (B), which was then followed again by a no-training follow-up phase (A^2).

In **chapter 4,** learning success was investigated among a group of forensic psychiatric patients for EEG-learning by means of theta/SMR neurofeedback training. We examined whether these patients were able to respond to the applied neurofeedback training protocol by examining their success in regulation of EEG magnitude in the SMR and theta frequency bands, and to which extent these changes in frequency bands were related to improvements in measures of impulsivity, craving, and drug intake. Patients were categorized as a 'neurofeedback-responder' when they showed both a successful upregulation of SMR magnitude and a successful downregulation of theta magnitude during at least 11 out of 19 sessions, as well as an average magnitude increase/decrease in the desired direction of 8% or higher by the end of the training. These criteria were

chosen based on the proposed protocol described in Weber, Köberl, Frank, and Doppelmayer (2011). Weber et al. (2011) proposed that EEG mean amplitude should change consistently across all sessions in the desired direction. As the study by Weber et al. (2011) was conducted with healthy participants, these criteria were adjusted to some extent to fit the population at hand. It was argued that a consistent change in mean EEG amplitude over all 19 sessions was probably too difficult to achieve for forensic psychiatric patients, but that a mean amplitude change over 60% of all sessions should be required in order to be qualified as a neurofeedback responder, resulting in 11 out of 19 sessions. The necessary average increase/decrease in the desired direction of 8% was not adjusted, as an average change in EEG magnitude of less than 8% might not be clinically relevant anymore. Results indicated that only four out of 19 patients (21%) were able to achieve successful regulation of both frequency bands by these criteria. Patients found it more difficult to regulate theta frequency than SMR frequency as evidence by the fact that 63% of patients managed to successfully increase the SMR magnitude, whereas only 37% of patients managed to decrease theta magnitude. As can be seen in **chapter 4**, Spearman's rho correlations between number of times patients successfully achieved up- or downregulation in the desired direction and height of average increase or decrease in the frequency band was significant at the $\alpha<0.01$ level in a single frequency (either theta or SMR) (theta: r=-.972, p<.01; SMR: r=.924, p<.01), as well as for the number of times SMR and theta were successfully regulated simultaneously (number of times SMR and theta were regulated simultaneously and average success SMR r=.619, p<.005, number of times SMR and theta were regulated simultaneously and average success theta r=-.697, p<.001) for all patients. A Wilcoxon Signed-ranks test indicated that results on the Barratt Impulsivity Scale -11 (BIS-11) and the Desire for Alcohol Questionnaire-SF (DAQ-SF) were significantly lower post-training (BIS-11: Z=-2.2, p<0.05, r=-.5; DAQ-SF: Z=1.982, p< 0.05, r=.45) for all patients, regardless of whether they had been qualified as neurofeedback responders or not. However, subsequent multiple linear regression analyses showed that the ability to consistently train frequency bands in the desired direction was not related to scores on impulsivity measures post-training. The variance in levels of craving post-training could partially be explained by whether patients could be categorized as responders, as this was related to the increase in SMR frequency but not to a decrease in theta frequency.

In **chapter 5**, the results of the RCT were presented. The RCT was conducted according to the design described in the study protocol in **chapter 3**. Patients eligible for participation according to the inclusion criteria were randomly assigned to either the neurofeedback training group or the treatment as usual (TAU) group. Forty-two patients completed all post-treatment measurements, of which 21 patients participated in the control group and 21 patients in the neurofeedback training group. Neurofeedback training lasted longer than the anticipated 10 weeks originally scheduled. This was due to holidays and planning issues, but also due to patients' inability to commit to two training sessions a week. Patients did not feel well enough to attend training sessions, were not motivated to participate, or caused aggressive incidents resulting in temporary placement on a specialized crisis unit. Participation in the study therefore lasted for an average of 14.1 (SD=5.32) weeks per patient. Randomization across treatment groups (neurofeedback training or TAU) was partially successful, as patients did not differ with regard to pre-treatment descriptive statistics, such as mean number of Axis I and II DSM-IV-TR diagnoses (neurofeedback training group M=4.52, SD=1.47; TAU group M=4.57, SD=1.63, t(40)=-.09, p=.38) or month in treatment prior to inclusion (neurofeedback training group M=91.90, SD=61.70; TAU group M=95.30,

SD=73.76, t(40)=-.16, *p*=.87). Surprisingly however, patients in the neurofeedback training group had significantly higher SMR magnitude pre-treatment (*Mdn*=1.00) than patients in the TAU only group (*Mdn*=.58), *U*=131.00, *p*=.02, *r*=.35).

Results of the RCT showed that patients who received neurofeedback training managed to increase SMR activity over the course of training (Time x Group effect for mean SMR magnitude *F*(1, 40)=5.47, *p*=.02, medium effect=.12), but failed to decrease theta activity (*F* (1, 40)=.14, *p*=.71, small effect=.00). Levels of drug craving showed a significant effect for Time (*F*(1, 40)= 6.23, *p*=.02, small effect=.02), but not for Time x Group (*F* (1, 40)=9.2, *p*=.34). The same was found for the 'motor impulsivity' subscale of the BIS-11, which showed a significant effect for Time (F(1, 40)=5.61, *p*=.02, medium effect=.03), but not for Time x Group (*F*(1, 40)=1.28, *p*=.28). Results for changes in drug use and number of commission errors post-treatment were not significant. Therefore, theta/SMR neurofeedback training was not superior to TAU with regards to behavioral improvements for the examined patient group.

Next to the RCT, a small sham-controlled clinical case series was employed in **chapter 6** to investigate interpersonal and individual differences between patients with regard to successful EEG-learning more deeply. As can be seen in the study protocol described in **chapter 3**, an ABA design was employed where a no-training baseline period (A^1) was followed by eight sessions of neurofeedback training (B^1), followed again by a no-training follow-up period (A^2). Four patients were randomly assigned to a real theta/SMR neurofeedback intervention, as compared to sham neurofeedback, where no frequency band was trained systematically. One patient in the sham neurofeedback condition dropped out before the start of the neurofeedback training period (B^1). Levels of impulsivity, drug craving, as well as drug intake were closely monitored over the course of this study. Results of this clinical case series were investigated by means of non-overlap of all pairs-scores (NAP-scores), which indicates data overlap between training and no-training phases in single-case studies and is seen as one of the best indexes to provide insight into the effect of intervention (Parker & Vannest, 2009). Also, simulation modeling analysis (SMA) was applied, testing change in level and slope of an outcome measure between two phases (Van Yperen, Veerman, & Bijl, 2017). Results of the clinical case study indicated that both patients in the real neurofeedback condition responded differently to the training in terms of change in outcome measures, with one of the patients receiving real theta/SMR neurofeedback benefitting more from the training than the other patient. This patient showed a significant decrease in impulsivity as measured with the BIS-11, with NAP-scores showing a strong effect (NAP=1.00, $p \leq 0.001$). When correcting for autocorrelation of NAP-scores, SMA-analysis revealed a significant level change (r=-.85, $p \leq .05$). Reduction in BIS-11 scores were not only observable in the total score of the BIS-11, but also in the subscales 'motor' and 'non-planning'. The subscale 'motor' showed a significant decrease over all phases (baseline phase A^1 versus follow-up phase A^2: NAP=1.00, $p \leq .001$; baseline phase A^1 versus training phase B: NAP=.95, $p \leq .001$; training phase B versus follow-up phase A^2: NAP=.92, $p \leq .001$). Results regarding levels of craving as measured with the DAQ-SF showed that this patient also had a significant reduction in DAQ-SF scores when comparing baseline phase A^1 with follow-up phase A^2 (NAP=1.00, $p \leq 0.001$). This effect was still highly significant when correcting for autocorrelation with SMA (level change r=-.96, $p \leq 0.001$). He also showed partial signs of neurofeedback learning, as he was able to increase SMR frequency (NAP=.75; $p \leq .05$) over the course of training, however, this effect did not remain significant when controlling for autocorrelation with SMA (r=.53, $p \geq .05$). Theta magnitude did

not change (NAP=.38, $p \geq .05$).

For the other patient who also received the real theta/SMR neurofeedback training, results indicated a significant reduction in BIS-11 total score when comparing baseline phase A^1 versus follow-up phase A^2 (NA =.82, $p \leq .001$), however, this effect did not remain significant when controlling for autocorrelation with SMA (r=-.59, p=≥.05). Results regarding levels of craving showed that this patient had a significant slope change (r=-.67, $p \leq .05$) that indicated an increase during baseline phase A^1, followed by a decrease in follow-up phase A^2. He showed no signs of EEG-learning, as SMR magnitude did not increase.

The patient in the sham neurofeedback condition did not show significant results with regard to a decrease in impulsivity, but rather showed an increase in BIS-11 scores by the end of follow-up phase A^2 (NAP=.22, $p<.001$), although this effect did not remain significant when controlling for autocorrelation with SMA levels of drug craving (A^1 versus A^2: NAP=.50, $p \geq .05$; A^1 versus B: NAP=.64, $p \geq .05$; B versus A^2: NAP=.60, $p \geq .05$). While not training SMR magnitude during the intervention, mean SMR magnitude showed a significant decrease by the end of follow-up phase A^2 (NAP=.25, $p<.05$), but this effect did not remain significant when controlling for autocorrelation with SMA. Theta magnitude increased significantly (NAP=.81, $p<0.01$). In sum, although all patients in the real neurofeedback condition received the same theta/SMR neurofeedback training protocol, one of the patients benefitted significantly more than the other patient from the training in terms of clinical improvements.

Reflection on findings - EEG-learning

In order to show the efficacy of neurofeedback training, it is a necessary first step to show that successful EEG-learning has occurred (Gruzelier, Egner, & Vernon, 2006; Zuberer, Brandeis, & Drechsler, 2015). The results of the current study show that the neurofeedback training protocol applied in this study did not result in the expected significant changes in EEG-frequency bands for 15 out of 19 patients who received theta/SMR neurofeedback in **chapter 4**, and for one of the two patients in the clinical case series. When comparing changes in frequency bands post-training to results from a control group, only the SMR magnitude showed a significant effect over time and group.

In the study described in **chapter 4**, the criteria set by Weber et al. (2011) were slightly adjusted as these criteria were originally established in a group of healthy college students. Forensic psychiatric patients may have more difficulties in learning new behavior and hence the criteria for EEG-learning were less strict. However, even with the adjusted criteria, only four out of 19 patients (21 %) managed to show evidence of EEG-learning. Also, not only did most of the patients not learn to increase or decrease their EEG magnitude in the desired direction, for six of the 19 patients investigated in **chapter 4**, a pattern of EEG magnitude change was observed that was opposite to the one the protocol was aiming for (decrease where an increase was the aim of the protocol and/or vice/versa). An important note to be made is that this study was the first in this target group, and that guidelines about which protocol best fits a group of forensic patients were not available.

In this study, conscious learning strategies applied by patients to regulate the video-games at hand with the neurofeedback intervention were not assessed. Therefore, the results with regard to EEG-learning found in this study must be interpreted with caution. Non-responder rates to neurofeedback training of about 15-20% are considered normal in research on so-called “brain-

computer illiteracy" (Blankertz et al., 2010). However, the fact that almost 80% of the forensic psychiatry patients in this study were classified as non-responders suggests that the theta/SMR neurofeedback protocol might have been too difficult for this special patient population. Rogala et al. (2016) have investigated previous studies on neurofeedback training and EEG-learning, and suggested that performance in neurofeedback training is related to the number of training parameters, with less training parameters resulting in better outcome measures. Apparently, for healthy participants or patients with less severe disorders, two EEG-training parameters are manageable, but these EEG-learning patterns seem to be incongruent with EEG-learning observed in the current population. It is possible that for forensic psychiatric patients, the fact that two frequency bands had to be adjusted simultaneously provided too big a challenge.

Another possible explanation is that for forensic psychiatric patients, EEG-learning might take different patterns to manifest than in other populations. EEG-learning might take more time to manifest, and may therefore require a higher number of sessions than the applied 20 sessions in the current RCT. However, performance in early sessions of neurofeedback training has been shown to predict performance in later sessions (e.g., Kübler, Neumann, Wilhelm, Hinterberger, & Birbaumer, 2004; Neumann & Bierbaumer, 2003; Weber et al., 2011). It therefore remains questionable whether more training sessions would have actually resulted in more EEG-learning in forensic psychiatric patients. Possibly, a more intense training protocol with sessions every day or every other day could perhaps have resulted in more training success. Rogala et al. (2016) found a tentative association between training success ratio and training intensity. It is debatable however, if a greater training intensity is actually possible in forensic patients because in general, forensic psychiatric patients tend to have low treatment motivation (e.g., Vandevelde, Broekaert, Schuyten, & van Hove, 2005), as well as lower capacity due to complex mental illness to comply with intense treatment schedules. In the RCT described in **chapter 5**, seven of the 29 patients dropped-out during the training due to lack of motivation to follow the planned 20 sessions. It is likely that even more patients would have dropped out if more sessions and/or a more intense training schedule had been required. Also, none of the patients was able to follow the training as originally scheduled, as training sessions twice a week were apparently too intensive for some patients. It remains uncertain why so few patients managed to successfully regulate the targeted EEG-frequencies. Psychological factors such as level of education, personality, personality disorders, psychopathology in general, mood, and age have also been proposed to influence the success of EEG-learning. Results of previous studies are, however, inconclusive. Some studies showed no association between the factors listed above (Hammer et al., 2012; Reichert, Kober, Neuper, & Wood, 2015), whereas other studies have demonstrated positive effects of motivational factors on learning performance (e.g., challenge and mastery confidence: Nijboer, Birbaumer, & Kübler, 2010). For all possible mechanisms assessed in previous studies, results must be examined with caution, especially because mechanisms that apply to a healthy population (or even a patient population with less sever psychopathology) cannot simply be applied to a forensic population. As can be seen from the systematic review of the literature in **chapter 2**, there are hardly any previous studies using neurofeedback training in populations comparable to the population at hand. Although the influence of psychopathology on patients ability to regulate EEG-frequencies has been investigated in some patient populations (e.g., in schizophrenia patients in the study by Schneider et al., 1992; or in psychopathic patients in the study by Konicar et al., 2015), it is unclear how this manifests in such a heterogeneous sample as the one in this study, where

patients suffered from multiple disorders and comorbid problems. Replication studies are needed, as well as studies on new EEG protocols for patients with severe mental illness to be able to make inferences about the precise nature of this association.

With regard to the current study, and patients' ability to regulate EEG-frequencies, we observed a difference between patients' ability to increase SMR magnitude and to decrease theta magnitude. For the patients in our study, it seemed easier to increase the SMR frequency than to decrease the theta frequency. The results reported in **chapter 4** show that more patients could have been qualified as responders if only SMR activity had been considered, and the results of the RCT described in **chapter 5** show a significant effect for SMR magnitude post-training, but not for theta magnitude. Of the three forensic psychiatric patients included in the clinical case-series described in **chapter 6**, one patient showed a trend towards successful SMR regulation, while none of the patients showed effects with regard to theta activity.

A few studies have identified predictors for successful SMR regulation. In studies by Reichert et al. (2015), and Blankertz et al. (2010), healthy participants' ability to enhance SMR power was related to their resting-state SMR power pre-training, and this SMR resting-state power was a predictor of learning performance of SMR. This phenomenon has been explained by very low levels of SMR found in some individuals, which make it difficult to record SMR activity on the scalp (Reichert et al., 2015), resulting in inadequate feedback during neurofeedback training trials. Surprisingly, patients in the intervention group of the RCT described in **chapter 5** had higher levels of SMR magnitude at baseline. We cannot explain why this baseline difference was observed, as participants were randomly assigned to either one of the two conditions, and did not differ with regard to any other baseline characteristic. However, this baseline difference could possibly be of influence in patients' ability to increase SMR activity. Possibly, the higher resting-state SMR power helped patients to be better able to further increase SMR over the course of training. However, resting-state SMR power was not used to investigate learning performance, so conclusions remain tentative.

When looking at an individual patient level by investigating the personality characteristics of single patients in the clinical case series reported in **chapter 6,** we could conclude that the patient who managed to increase SMR activity and benefitted most from neurofeedback training, was the same patient with the most severe cluster B personality disorders, presenting with a diagnosis of borderline, antisocial and histrionic personality disorder. This patient showed the highest score on impulsivity at the start of the training compared to the other two patients, but was apparently more able to reduce impulsivity over the course of training. He also had the least amount of SUD diagnoses and showed the lowest magnitude of SMR in the first two sessions as compared to the other patients.

It has been suggested that the feedback-learning of EEG parameters is comparable to common motor learning (Hammer et al., 2012; Lang & Twentyman, 1976), and that participants with better visual-motor coordination abilities seem to learn better SMR regulation (Hammer et al., 2012). Participants' ability to focus and concentrate at the task at hand has also been shown to be of influence for SMR training performance (Hammer et al., 2012). This point might underline the difficulties that treatment supervisors face when it comes to applying neurofeedback training in forensic treatment settings, as highly impulsive patients have more trouble to sit still, and to focus and concentrate on the task at hand due to the disorders they seek treatment for.

It seems unlikely that the differences between SMR and theta band regulation were due to the fact

that participants found it easier to up-train a brain frequency rather than to down-train a frequency band. In a study by Blankertz et al. (2010), SMR frequency was trained, but unlike the approach of the current study, participants were instructed to systematically reduce SMR power over the course of training. Still, about 23.5% of participants were qualified as non-responders. It appears that either the theta frequency possesses special challenges for regulation with neurofeedback training, or regulating more than one parameter is already too difficult.
In sum, the applied theta/SMR neurofeedback protocol only resulted in partial effects on EEG-frequencies, as only significant changes in the SMR frequency could be found post-training. It remains speculative as to which factors led to the results found in this study and this should be further investigated in future studies.

Reflections on findings – behavioral effects of neurofeedback training
Results of neurofeedback training should also adhere to the condition of interpretability (Zoefel, Huster, & Herrmann, 2010). That is, before applying neurofeedback, the targeted EEG-frequency bands should be associated with certain cognitive functions in order to increase the probability of reliable behavioral effects post-training. A central hypothesis in neurofeedback research is that the normalization of deviant EEG-frequencies leads to improvements in behavior. In the current thesis, results on behavioral measures were mixed. In the study described in **chapter 4**, patients showed a decrease in impulsivity as assessed with the BIS-11, as well as in drug craving and number of positive drug testing. However, when these patients were compared to patients in the TAU-only group in **chapter 5**, none of the measurements showed a significant decrease post-training for the neurofeedback training group that was superior to patients in the TAU-only group. When linking results on EEG-regulation to effects on a behavioral level, it seemed that only changes in SMR-activity were related to changes in behavioral outcome measures.
In **chapter 4**, only a decrease in levels of craving post-training was associated with the average increase in SMR-activity. In the clinical case series presented in **chapter 6**, self-report scores of impulsivity did decrease for one of the patients who also showed a significant increase in mean SMR magnitude. However, the association between these two measures was not assessed, so no conclusions can be drawn about the association between SMR increase and decrease in self-reported impulsivity for this patient.
Paradoxically, there are many studies that report improvements in clinical symptoms while no changes on a cortical level could be found. Gevensleben et al. (2014) for example used a slow cortical potential neurofeedback training in children with high levels of impulsivity due to ADHD, and they report a reduction in impulsivity symptoms of 20% post-training, while participants were only able to partially learn the neurofeedback paradigm. Liechti et al. (2012) found no changes in theta and/or beta frequency bands, but observed improvements in impulsivity post-training. The study by Arani, Rostami, and Nostratabadi (2010) found only a partial change in frequency bands in the desired direction, but did find significant improvements in symptoms of SUD, such as desire to use and relief from withdrawal. Behavioral effects have even been found when participants regulated their cortical activity in the opposite direction as intended, as Arns et al. (2012) found improvements in levels of impulsivity, even though SMR magnitude decreased instead of increased. These findings raise the question whether unspecific effects of neurofeedback training possibly play a role in explaining effects of the intervention. It has frequently been suggested that much of the behavioral effects observed for neurofeedback

training result from patient-therapist interaction, learning to sit still and positive expectations of outcomes (Barth, Mayer, Strehl, Fallgatter, & Ehlis, 2017).
Other studies report outcomes on behavioral measures that are comparable to the outcomes reported in the current study. In Schönenberg et al. (2017), impulsivity levels decreased equally for participants in a neurofeedback training group as for participants in the sham or meta-cognitive therapy group. In a study by Bink, Nieuwenhuizen, Popma, Bongers and van Boxtel (2015), hyperactivity/impulsivity levels in ADHD participants decreased equally for participants in the control group and the intervention group. Most importantly, the studies by Schönenberg et al. (2017) and Bink et al. (2015) also found no changes in EEG-frequencies due to neurofeedback training. No changes could be observed in participants' theta/beta ratio by the end of the training in Schönenberg et al. (2017), and in Bink et al. (2015), none of the frequency bands showed an effect over time. In a sample of alcohol dependent patients, Lackner et al. (2016) found no significant improvements on craving levels, as well as non-specific symptoms such as depressive and psychiatric symptoms. Changes in alpha and theta frequency were only significant by trend.
In conclusion, the current study did not find results on a behavioral level that can be linked to the employed theta/SMR neurofeedback training protocol. As mentioned above, only partial changes in EEG-frequencies in this study could be observed. Changes in theta frequency post-training were not found to be related to changes on behavioral outcome measures, so it seems unlikely that more improvements in the intended EEG-frequency bands would have resulted in more improvements on a behavioral level.

Limitations of the current study

As with every research, there are some limitations of the current study. First of all, we did not apply a pilot study to test for possible omissions with the applied neurofeedback training protocol. A pilot study might have helped to assess the apparent difficulties patients had in learning the theta/SMR neurofeedback training protocol used in this study early on. The main reason not to employ a pilot study was the difficulties we expected concerning patient recruitment. Forensic psychiatric patients are a difficult patient group when it comes to conducting large randomized trials, partly because of a lack of motivation and heightened levels of suspiciousness about possible negative influences of outcome measures in legal documents. We did our best to inform patients about their right to resign from the study at any point during participation without any negative consequences, and yet found it difficult to include more than the necessary 42 patients to reach the necessary power.
Next, except for the clinical case series in **chapter 6**, the studies described in this thesis were not sham controlled. While sham controlled studies are considered the highest possible standard for assessing the efficacy of an intervention, it is questionable whether this approach is the most suitable for assessing the efficacy for neurofeedback in such a vulnerable patient population. First, some learning of EEG-regulation cannot be ruled out when using a sham condition where assumingly irrelevant frequency bands are trained. Second, a placebo condition does not allow for the assessment of the indirect non-specific effects mentioned above. Most importantly, the use of a placebo or sham condition raises ethical questions when it comes to applying these conditions to forensic psychiatric patients. Given that these patients lack motivation to participate in treatment as it is, but are also often times not able to undergo long treatment sessions due to their clinical symptoms, forcing a large number of mock training sessions on these patients might

further diminish their motivation to participate in treatment.
Another limitation of the current study is the fact that effects were not controlled for possible medication intake of patients. Stimulant medications such as methylamphetamine and/or dexamphetamine have shown to normalize certain EEG-frequencies, and lead to a reduction of theta activity and an increase in low beta band activity (e.g., Clarke, Barry, McCarthy, Selikowitz, Brown, & Croft, 2003; Saletu, Anderer, & Saletu-Zyhlarz, 2006). Other studies reported no differences with regard to effects of neurofeedback training on the core symptoms of ADHD (inattention, hyperactivity and impulsivity) between participants medicated with methylphenidate and participants without medication (Arns, de Ridder, Strehl, Breteler, & Coenen, 2009). Although type of medication and dosage were assumed to be stable over the course of the current study, and generally, patients had been on their particular medication for quite a while, it is possible that different types of medication will influence baseline EEG-activity and therefore also patients' ability to regulate their own EEG-activity. Patients might not be able to regulate their EEG-activity beyond what is already established by medication use. Additional research is needed to investigate effects of different types of medication and medication dosage on EEG-learning. However, with regard to medication intake, an important note must be made: It can be considered unethical to ask patients to stop medication intake for the sake of an intervention of which the clinical benefits are still uncertain. Given the special setting of the current research, terminating medication intake could also be considered irresponsible, as this might have increased chances for patients to experience more symptoms that could have increased risks for aggressive and violent behavior.
It is possible that medication intake of some patients also affected behavioral outcome measures. Some common antipsychotic medications like risperidone, olanzapine or clozapine are hypothesized to affect levels of craving (Machielsen et al., 2012). Machielsen et al. (2012) for example found diminished levels of craving for cannabis dependent schizophrenic patients using risperidone, as well as van Nimwegen et al. (2008) who found a decrease in craving levels for risperidone and olanzapine. More than 50% of patients in the RCT described in **chapter 5**, and in the study in **chapter 4** were diagnosed with schizophrenia or related disorders. While the use of medication was not assessed, it is very likely that these patients received one of the antipsychotic medications described above, and that these patients report less craving due to their medication.

Clinical implications and directions for future studies
Based on the results of the studies in this thesis, it can be concluded that the applied theta/SMR neurofeedback protocol in the current form is only suitable for a small group of forensic psychiatric patients. The results of this study suggest that forensic psychiatric patients with SUD and comorbid disorders are not able to simultaneously regulate their theta as well as SMR magnitude. Future research should focus on identifying interpersonal mechanisms that predict successful learning of EEG-activity in general, as this can be seen as a necessary condition that must be met in order to establish improvements on clinical outcome measures. More specifically, future research should focus on a) whether forensic psychiatric patients are able to train more than one EEG-frequency at a time and b) whether differences in EEG-learning abilities can be traced back to specific EEG-frequency bands. This study only made use of one specific neurofeedback training protocol, while many other protocols can be considered. Possibly, a SMR-only neurofeedback training protocol is better suited for forensic psychiatric patients instead of a protocol that trains two

parameters at once. There are also more types of neurofeedback training protocols to consider, which might be able to achieve better effects for this patient population. However, specifically for highly impulsive patients, the meta-analysis by Arns et al. (2009) found no differential effects for different neurofeedback training protocols such as theta/beta training, theta/SMR or training of the slow cortical potential on impulsivity, but the study did not investigate differential effects of the different protocols on EEG-frequency bands. Possibly, other training protocols will achieve more EEG-learning in forensic psychiatric patients. Future studies should then also investigate whether specific patient populations are better able to regulate specific brain frequencies, and to what extent this affects clinical outcome measures. Patients who are not able to regulate brain frequencies then need to be offered different forms of treatment that are better suited.

As mentioned above, some studies have suggested ways to predict patients' EEG-performance from baseline characteristics or performance during early sessions, but these lines of research need to be investigated further to establish clear performance indicators. Especially for the patients studied in this thesis, it is crucial to not force a large number of training sessions upon them, which will most likely not help them, and therefore diminish their motivation for treatment even further. "Finding possible predictors that are linked to underlying mechanisms of cortical learning will help to identify important factors that should be taken into account to promote neurofeedback efficacy" (Alkoby, Abu-Rmileh, Shriki, & Todder, 2017, p.4).

Halligan and David (2001) have termed the phrase 'cognitive neuropsychiatry', which attempts to establish the functional organization of psychiatric disorders within a framework of cognitive neuropsychiatry and psychopathology, and linking this framework to relevant brain structures and their pathology in order to better understand psychiatric conditions. Within this framework, they emphasize the importance of clinical case studies. They argue that, averaging symptoms over a whole patient group might neglect important individual differences, as psychopathology or brain damage might manifest differently between individuals. Concerning our current study, applying a one-size-fits-all neurofeedback training protocol in order to be able to compare effects of a treatment for a whole group of patients might not have been the most suitable approach, given that in this specific patient population, clinical symptoms and disorders manifest in a highly variable way. The different comorbidities and SUD, as well as varying forms of medication, might lead to different manifestations in brain and behavior as compared to patient populations where medication intake is restricted, and patients with comorbidities are excluded from participation. For this thesis, the decision to not restrict inclusion criteria any further had been well thought through. First, restricting participation for the study to patients without an axis I disorders for example, would have seriously diminished our sample size, which wasn't an option since the research group was already small. Although our response rate was quite large with 63%, and the drop-out rate for the neurofeedback training group was rather low (27.5%), we still encountered difficulties when recruiting patients for participation. Of all patients residing in the treatment facility who were diagnosed with a SUD, more than 30% were not eligible for participation because of pending release or transfer from the treatment facility, or clinical symptoms too severe to be able to participate (such as psychotic symptoms). Also, many patients were hesitant to undergo 20 sessions of an intervention of which the efficacy has yet to be proven. Especially for patients with schizophrenia, the thought of participating in an intervention where electrodes are placed on the scalp in order to record brain activity was often times a scary thought that prevented them from signing up for participation. Notwithstanding the power requirement was met, the

sample size in the RCT was quite small, yet, it was comparable to most of the studies assessed in **chapter 2** (with the exception of the study by Konicar et al., 2017). Second, heightened levels of impulsivity can be found in almost all forensic psychiatric patients, regardless of diagnosis. The aim of this thesis therefore was to assess the applicability and efficacy of neurofeedback for forensic psychiatric patients with SUD, not only for a specific subset of forensic patients.

In recent years, the approach of personalized medicine has received increasing attention in psychiatric treatment and research. In line with that, studies have emphasized the benefits of QEEG-guided neurofeedback protocols, in which baseline EEG-deviations are assessed, and neurofeedback training protocols are then tailored to the specific deviations found on pre-training assessment, as well as to the specific clinical complaints of the patient. This approach might also treat more than one specific clinical complaint and improve well-being in general, as EEG-deviations can result in a number of subjective complaints. Investigating the effects of neurofeedback training with a clinical case study could then provide practitioners with valuable information about interpersonal differences that they can apply in subsequent cases.

The success of neurofeedback training for forensic patients might also lie more in secondary factors such as dealing with stress and/or anxiety, which are especially pronounced during the first phases of recovery (Scott, Kaiser, Othmer, & Sideroff, 2005), rather than normalizing (all) EEG-deviations. Previous studies have shown that patients who underwent neurofeedback training stayed in treatment significantly longer than patients who did not (e.g., Scott et al., 2005). For forensic psychiatric patients, treatment progress will almost certainly benefit from treating attention deficit and/ or impulsivity (Keith, Rapgay, Theordore, Schwartz, & Ross, 2015).

Concluding remarks

Suffering from addiction is a life changing clinical disease, affecting every part of an individual's life and his environment. Decades of studies with individuals suffering from substance use disorder have shown that addiction recovery is not sobriety alone. High rates of comorbid disorders, PTSS, childhood (sexual) abuse and trauma seem to play an important part in present attempts to recovery (Vigilant, 2008), and these factors are also present in many forensic patients. The phrase 'multiple recoveries' has been termed to describe the many stages of reparations involved (Giddens, 1991) in order for individuals to recover from the psychological, physical and emotional strains of addiction (Vigilant, 2008). For forensic psychiatric patients, the road to recovery may provide even more challenges, and gaining control over addiction is a crucial step towards starting a new life after inpatient treatment. Substance abuse treatment, where the treatment matches a patient's etiology and maintaining factors should be more effective than a generalized substance abuse treatment aimed to fit a wide variety of patients (Tomko, Bountress, & Gray, 2016). Neurofeedback training may just be one of the interventions employed in order to achieve recovery, but it can never stand alone. Future studies will hopefully help to shed light on which patients will be able to benefit most from the training, but even so, integrating this treatment into a wider treatment approach, where impulsive behavior is understood as affecting not only addictive behavior, but also chances for violence, aggression and self-harming behavior, will give forensic psychiatric patients the highest chances for successful recovery.

References

American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders* (4th ed., text rev.). Washington, DC: Author.

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). Washington, DC: Author

Albein-Urios, N., Pilatti, A., Lozano, Ó., Martínez-González, J. M., & Verdejo-García, A. (2014). The value of impulsivity to define subgroups of addicted individuals differing in personality dysfunction, craving, psychosocial adjustment, and wellbeing: A latent class analysis. *Archives of Clinical Neuropsychology, 29*(1), 38-46. doi:10.1093/arclin/act072

Alkoby, O., Abu-Rmileh, A., Shriki, O., & Todder, D. (2017). Can we predict who will respond to neurofeedback? A review of the inefficacy problem and exiting predictors for successful EEG Neurofeedback learning. *Neuroscience, 15(378), 155-164*. doi:10.1016/j.neuroscience.2016.12.050

Alniak, I., Erkiran, M., & Mutlu, E. (2016). Substance use is a risk factor for violent behavior in male patients with bipolar disorder. *Journal of Affective Disorders, 193*, 89-93. doi:10.1016/j.jad.2015.12.059

Alper, K. R., Prichep, L. S., Kowalik, S., Rosenthal, M. S., & John, E. R. (1998). Persistent QEEG abnormality in crack cocaine users at 6 months of drug abstinence. *Neuropsychopharmacology, 19*(1), 1-9. doi:10.1016/S0893-133X(97)00211-X

Arani, F. D., Rostami, R., & Nostratabadi, M. (2010). Effectiveness of neurofeedback training as a treatment for opioid-dependent patients. *Clinical EEG and Neuroscience, 41*(3), 170-7. doi: 10.1177/155005941004100313

Arns, M., de Ridder, S., Strehl, U., Breteler, M., & Coenen, A. (2009). Efficacy of Neurofeedback Treatment in ADHD: the Effects on Inattention, Impulsivity and Hyperactivity: A meta-analysis. *Clinical EEG and Neuroscience, 40*(3), 180-189. doi:10.1177/155005940904000311

Arns, M., Drinkenburg, W., & Kenemans, J. L. (2012). The effects of QEEG-informed neurofeedback in ADHD: An open-label pilot study. *Applied Psychophysiology and Biofeedback, 37*(3), 171-180. doi:10.1007/s10484-012-9191-4

Arns, M., Heinrich, H., & Strehl, U. (2014). Evaluation of neurofeedback in ADHD: The long and winding road. *Biological Psychology, 95*, 108-115. doi:10.1016/j.biopsycho.2013.11.013

Bakhshayesh, A. R., Hänsch, S., Wyschkon, A., Rezai, M. J., & Esser, G. (2011). Neurofeedback in ADHD: A single-blind randomized controlled trial. *European Child & Adolescent Psychiatry, 20*(9), 481-491. doi:10.1007/s00787-011-0208-y

Barry, R. J., Johnstone, S. J., & Clarke, A. R. (2003). A review of electrophysiology in attention-deficit/hyperactivity disorder: II event-related potentials. *Clinical Neurophysiology, 114*(2), 184-198. doi:10.1016/S1388-2457(02)00363-2

Barth, B., Mayer, K., Strehl, U., Fallgatter, A. J., & Ehlis, A. (2017). EMG biofeedback training in adult attention-deficit/hyperactivity disorder: An active (control) training? *Behavioural Brain Research, 329*, 58-66. doi:10.1016/j.bbr.2017.04.021

Bates, M. E., Bowden, S. C., & Barry, D. (2002). Neurocognitive impairment associated with alcohol use disorders: Implications for treatment. *Experimental and Clinical Psychopharmacology, 10*(3), 193-212. doi:10.1037/1064-1297.10.3.193

Bechara, A. (2005). Decision making, impulse control and loss of willpower to resist drugs: A neurocognitive perspective. *Nature Neuroscience, 8*(11), 1458-1463. doi:10.1038/nn1584

Beresford, T., Buchanan, J., Thumm, E. B., Emrick, C., Weitzenkamp, D., & Ronan, P. J. (2017). Late reduction of cocaine cravings in a randomized, double-blind trial of aripiprazole vs perphenazine in schizophrenia and comorbid cocaine dependence. *Journal of Clinical Psychopharmacology, 37*(6), 657-663. doi:10.1097/JCP.0000000000000789

Bink, M., van Nieuwenhuizen, C., Popma, A., Bongers, I. L., & van Boxtel, G. J. M. (2015). Behavioral effects of neurofeedback in adolescents with ADHD: A randomized controlled trial. *European Child & Adolescent Psychiatry, 24*(9), 1035-1048. doi:10.1007/s00787-014-0655-3

Birbaumer, N., Elbert, T., Canavan, A., & Rockstroh, B. (1990). Slow potentials of the cerebral cortex and behavior. *Physiological Reviews, 70*(1), 1-41. doi:10.1152/physrev.1990.70.1.1

Black, R. A., Serowik, K. L., & Rosen, M. I. (2009). Associations between impulsivity and high risk sexual behaviors in dually diagnosed outpatients. *The American Journal of Drug and Alcohol Abuse, 35*(5), 325-328. doi:10.1080/00952990903075034

Blankertz, B., Sannelli, C., Halder, S., Hammer, E. M., Kübler, A., Müller, K., & Dickhaus, T. (2010). Neurophy-

siological predictor of SMR-based BCI performance. *Neuroimage, 51*(4), 1303-1309. doi:10.1016/j.neuroimage.2010.03.022

Bogaerts, S., Spreen, M., Ter Horst, P. & Gerlsma, C. (2018). Predictive Validity of the HKT-R Risk Assessment Tool: Two and Five-year Violent Recidivism in a Nationwide Sample of Dutch Forensic Psychiatric Patients. *International Journal of Offender Therapy and Comparative Criminology, 62*(8): 2259-2270. doi:10.1177/0306624X17717128

Boles, S. M., & Miotto, K. (2003). Substance and violence: A review of the literature. *Aggression and Violent Behavior, 8*(2), 155-174. doi:10.1016/S1359-1789(01)00057-X

Boog, M., Goudriaan, A. E., van, d. W., Deuss, H., & Franken, I. H. A. (2013). The concepts of rash impulsiveness and reward sensitivity in substance use disorders. *European Addiction Research, 19*(5), 261-268. doi:10.1159/000346178

Borckardt, J.J. SMA Time Series Analysis Program for Short time Series Data Streams. Version 8.3.3. (2006). Retrieved from http://www.clinicalresearcher.org/software.htm

Borckardt, J. J., Nash, M. R., Murphy, M. D., Moore, M., Shaw, D., & O'Neil, P. (2008). Clinical practice as natural laboratory for psychotherapy research: A guide to case-based time-series analysis. *American Psychologist, 63*(2), 77-95. doi:10.1037/0003-066X.63.2.77

Bornovalova, M. A., Levy, R., Gratz, K. L., & Lejuez, C. W. (2010). Understanding the heterogeneity of BPD symptoms through latent class analysis: Initial results and clinical correlates among inner-city substance users. *Psychological Assessment, 22*(2), 233-245. doi:10.1037/a0018493

Bozkurt, M., Evren, C., Can, Y., Evren, B., Cetingok, S., & Yilmaz, A. (2014). Relationships of personality dimensions with impulsivity in alcohol-dependent inpatient men. *Nordic Journal of Psychiatry, 68*(5), 316-322. doi:10.3109/08039488.2013.830772

Bresnahan, S. M., & Barry, R. J. (2002). Specificity of quantitative EEG analysis in adults with attention deficit hyperactivity disorder. *Psychiatry Research, 112*(2), 133-144. doi:10.1016/S0165-1781(02)00190-7

Byiers, B. J., Reichle, J., & Symons, F. J. (2012). Single-subject experimental design for evidence-based practice. *American Journal of Speech-Language Pathology, 21*(4), 397-414. doi:10.1044/1058-0360(2012/11-0036)

Cantor, D. S. (1999). An overview of quantitative EEG and its applications to neurofeedback. In J. R. Evans, & A. Abarbanel (Eds.), (pp. 3-27). San Diego, CA: Academic Press. doi:10.1016/B978-012243790-8/50002-X

Carmody, D. P., Radvanski, D. C., Wadhwani, S., Sabo, M. J., & Vergara, L. (2001). EEG biofeedback training and attention-deficit/hyperactivity disorder in an elementary school setting. *Journal of Neurotherapy, 4*(3), 5-27. doi:10.1300/J184v04n03_02

Casher, M. I. (2013). Commentary: Complex case: A biofeedback intervention to control impulsiveness in a severely personality disordered forensic patient by rick Howard, Klaus Schellhorn and John Lumsden. *Personality and Mental Health, 7*(2), 174-176. doi:10.1002/pmh.1232

Caswell, A. J., Bond, R., Duka, T., & Morgan, M. J. (2015). Further evidence of the heterogeneous nature of impulsivity. *Personality and Individual Differences, 76*, 68-74. doi:10.1016/j.paid.2014.11.059

Charney, D. A., Zikos, E., & Gill, K. J. (2010). Early recovery from alcohol dependence: Factors that promote or impede abstinence. *Journal of Substance Abuse Treatment, 38*(1), 42-50. doi:10.1016/j.jsat.2009.06.002

Clark, L., Robbins, T. W., Ersche, K. D., & Sahakian, B. J. (2006). Reflection impulsivity in current and former substance users. *Biological Psychiatry, 60*(5), 515-522. doi:10.1016/j.biopsych.2005.11.007

Clarke, A. R., Barry, R. J., McCarthy, R., Selikowitz, M., Brown, C. R., & Croft, R. J. (2003). Effects of stimulant medications on the EEG of children with attention-deficit/hyperactivity disorder predominantly inattentive type. *International Journal of Psychophysiology, 47*(2), 129-137. doi:10.1016/S0167-8760(02)00119-8

Clarke, A. R., Barry, R. J., Dupuy, F. E., Heckel, L. D., McCarthy, R., Selikowitz, M., & Johnstone, S. J. (2011). Behavioural differences between EEG-defined subgroups of children with attention-Deficit/Hyperactivity disorder. *Clinical Neurophysiology, 122*(7), 1333-1341. doi:10.1016/j.clinph.2010.12.038

Cohen, J. (1977). *Statistical power analysis for the behavioral sciences, rev ed*. Hillsdale, NJ: Lawrence Erlbaum Associates, Inc.

Convit, A., Czobor, P., & Volavka, J. (1991). Lateralized abnormality in the EEG of persistently violent psychiatric inpatients. *Biological Psychiatry, 30*(4), 363-370. doi:10.1016/0006-3223(91)90292-T

Cortese, S., Ferrin, M., Brandeis, D., Holtmann, M., Aggensteiner, P., Daley, D., & Sonuga-Barke, E. (2016). Neurofeedback for attention-deficit/hyperactivity disorder: Meta-analysis of clinical and neuropsychological outcomes from randomized controlled trials. *Journal of the American Academy of Child & Adolescent*

Psychiatry, 55(6), 444-455. doi:10.1016/j.jaac.2016.03.007
Courtney, K. E., Ashenhurst, J., Bacio, G., Moallem, N., Bujarski, S., Hartwell, E., & Ray, L. A. (2013). Craving and subjective responses to alcohol administration: Validation of the desires for alcohol questionnaire in the human laboratory. *Journal of Studies on Alcohol and Drugs, 74*(5), 797-802. doi:10.15288/jsad.2013.74.797
Crews, F. T., & Boettiger, C. A. (2009). Impulsivity, frontal lobes and risk for addiction. *Pharmacology, Biochemistry and Behavior, 93*(3), 237-247. doi:10.1016/j.pbb.2009.04.018
Criswell, E. (1995). *Biofeedback and somatics: Toward personal evolution*. Novato, CA: Freeperson Press.
Dackis, C. A., & O'Brien, C. P. (2001). Cocaine dependence: A disease of the brain's reward centers. *Journal of Substance Abuse Treatment, 21*(3), 111-117. doi:10.1016/S0740-5472(01)00192-1
deBeus, R. J., & Kaiser, D. A. (2011). Neurofeedback with children with attention deficit hyperactivity disorder: A randomized double-blind placebo-controlled study. In R. Coben, & J. R. Evans (Eds.), (pp. 127-152). San Diego, CA: Elsevier Academic Press. doi:10.1016/B978-0-12-382235-2.00005-6
de Wit, H., & Richards, J. B. (2004). Dual determinants of drug use in humans: Reward and impulsivity. In R. A. Bevins, & M. T. Bardo (Eds.), (pp. 19-55). Lincoln, NE: University of Nebraska Press.
De la Fuente, J. M., Tugendhaft, P., & Mavroudakis, N. (1998). Electroencephalographic abnormalities in borderline personality disorder. *Psychiatry Research, 77*(2), 131-138. doi:10.1016/S0165-1781(97)00149-2
Dehghani-Arani, F., Rostami, R., & Nadali, H. (2013). Neurofeedback training for opiate addiction: Improvement of mental health and craving. *Applied Psychophysiology and Biofeedback, 38*(2), 133-141. doi:10.1007/s10484-013-9218-5
Dekker, M. K. J., Sitskoorn, M. M., Denissen, A. J. M., & van Boxtel, Geert J. M. (2014). The time-course of alpha neurofeedback training effects in healthy participants. *Biological Psychology, 95*, 70-73. doi:10.1016/j.biopsycho.2013.11.014
Demos, J. N. (2005). *Getting started with neurofeedback*. New York, NY: W W Norton & Co.
Doehnert, M., Brandeis, D., Straub, M., Steinhausen, H., & Drechsler, R. (2008). Slow cortical potential neurofeedback in attention deficit hyperactivity disorder: Is there neurophysiological evidence for specific effects? *Journal of Neural Transmission, 115*(10), 1445-1456. doi:10.1007/s00702-008-0104-x
Doppelmayr, M., & Weber, E. (2011). Effects of SMR and theta/beta neurofeedback on reaction times, spatial abilities, and creativity. *Journal of Neurotherapy, 15*(2), 115-129. doi:10.1080/10874208.2011.570689
Dougherty, D. M., Mathias, C. W., Marsh-Richard, D., Furr, R. M., Nouvion, S. O., & Dawes, M. A. (2009). Distinctions in behavioral impulsivity: Implications for substance abuse research. *Addictive Disorders & their Treatment, 8*(2), 61-73. doi:10.1097/ADT.0b013e318172e488
Drechsler, R., Straub, M., Doehnert, M., Heinrich, H., Steinhausen, H., & Brandeis, D. (2007). Controlled evaluation of a neurofeedback training of slow cortical potentials in children with attention Deficit/Hyperactivity disorder (ADHD). *Behavioral and Brain Functions, 3*. doi:10.1186/1744-9081-3-35
Dugré, J. R., Dellazizzo, L., Giguère, C., Potvin, S., & Dumais, A. (2017). Persistency of cannabis use predicts violence following acute psychiatric discharge. *Frontiers in Psychiatry, 8*. doi:10.3389/fpsyt.2017.00176
Duke, A. A., Smith, K. M. Z., Oberleitner, L. M. S., Westphal, A., & McKee, S. A. (2018). Alcohol, drugs, and violence: A meta-meta-analysis. *Psychology of Violence, 8*(2), 238-249. doi:10.1037/vio0000106
Duric, N. S., Aßmus, J., & Elgen, I. B. (2014). Self-reported efficacy of neurofeedback treatment in a clinical randomized controlled study of ADHD children and adolescents. *Neuropsychiatric Disease and Treatment, 10* , ArtID: 1645-1654.
Edens, J. F., Kelley, S. E., Lilienfeld, S. O., Skeem, J. L., & Douglas, K. S. (2015). DSM-5 antisocial personality disorder: Predictive validity in a prison sample. *Law and Human Behavior, 39*(2), 123-129. doi:10.1037/lhb0000105
Egner, T., & Gruzelier, J. H. (2004). EEG biofeedback of low beta band components: Frequency-specific effects on variables of attention and event-related brain potentials. *Clinical Neurophysiology, 115*(1), 131-139. doi:10.1016/S1388-2457(03)00353-5
Ellingson, R. J. (1954). The incidence of EEG abnormality among patients with mental disorders of apparently nonorganic origin: A critical review. *The American Journal of Psychiatry, 111*, 263-275. doi:10.1176/ajp.111.4.263
Enriquez-Geppert, S., Huster, R. J., Scharfenort, R., Mokom, Z. N., Zimmermann, J., & Herrmann, C. S. (2014). Modulation of frontal-midline theta by neurofeedback. *Biological Psychology, 95*, 59-69. doi:10.1016/j.biopsycho.2013.02.019

Enticott, P. G., Ogloff, J. R. P., Bradshaw, J. L., & Fitzgerald, P. B. (2008). Cognitive inhibitory control and self-reported impulsivity among violent offenders with schizophrenia. *Journal of Clinical and Experimental Neuropsychology, 30*(2), 1-6. doi:10.1080/13803390701290055

Evenden, J. L. (1999). Varieties of impulsivity. *Psychopharmacology, 146*(4), 348-361. doi:10.1007/PL00005481

Faul, F., Erdfelder, E., Lang, A., & Buchner, A. (2007). GPower 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behavior Research Methods, 39*(2), 175-191. doi:10.3758/BF03193146

Fazel, S., & Danesh, J. (2002). Serious mental disorder in 23000 prisoners: a systematic review of 62 surveys. *The Lancet, 359*, 545-550. doi: 10.1016/S0140-6736(02)07740-1

Fenton, G. W., Fenwick, P. B., Dollimore, J., Dunn, T. L., & Hirsch, S. R. (1980). EEG spectral analysis in schizophrenia. *The British Journal of Psychiatry, 136*, 445-455. doi:10.1192/bjp.136.5.445

Fielenbach, S., Donkers, F. C. L., Spreen, M., & Bogaerts, S. (2017). Neurofeedback as a Treatment for Impulsivity in a Forensic Psychiatric Population With Substance Use Disorder: Study Protocol of a Randomized Controlled Trial Combined With an N-of-1 Clinical Trial. *JMIR Research Protocols, 6(1)*:e13. doi: 10.2196/resprot.6907

Fielenbach, S., Donkers, F. C. L., Spreen, M., & Bogaerts, S. (2018a). The ability of forensic psychiatric patients with substance use disorder to learn Neurofeedback. *International Journal of Forensic Mental Health*. doi:10.1080/14999013.2018.1485187

Fielenbach, S., Donkers, F. C. L., Spreen, M., Visser, H. A., & Bogaerts, S. (2018b). Neurofeedback training for psychiatric disorders associated with criminal offending: A review. *Frontiers in Psychiatry, 8.* doi:10.3389/fpsyt.2017.00313

Fillmore, M. T. (2003). Drug abuse as a problem of impaired control: Current approaches and findings. *Behavioral and Cognitive Neuroscience Reviews, 2*(3), 179-197. doi:10.1177/1534582303257007

Fillmore, M. T., & Rush, C. R. (2006). Polydrug abusers display impaired discrimination-reversal learning in a model of behavioural control. *Journal of Psychopharmacology, 20*(1), 24-32. doi:10.1177/0269881105057000

Flor, H., Birbaumer, N., Hermann, C., Ziegler, S., & Patrick, C. J. (2002). Aversive pavlovian conditioning in psychopaths: Peripheral and central correlates. *Psychophysiology, 39*(4), 505-518. doi:10.1017/S0048577202394046

Forth, A. E., & Hare, R. D. (1989). The contingent negative variation in psychopaths. *Psychophysiology, 26*(6), 676-682. doi:10.1111/j.1469-8986.1989.tb03171.x

Franken, I. H. A. (2003). Drug craving and addiction: Integrating psychological and neuropsychopharmacological approaches. *Progress in Neuro-Psychopharmacology & Biological Psychiatry, 27*(4), 563-579. doi:10.1016/S0278-5846(03)00081-2

Franken, I. H. A., Rosso, M., & van Honk, J. (2003). Selective memory for alcohol cues in alcoholics and its relation to craving. *Cognitive Therapy and Research, 27*(4), 481-488. doi:10.1023/A:1025480615623

Fuchs, T., Birbaumer, N., Lutzenberger, W., Gruzelier, J. H., & Kaiser, J. (2003). Neurofeedback treatment for attention-deficit/hyperactivity disorder in children: A comparison with methylphenidate. *Applied Psychophysiology and Biofeedback, 28*(1), 1-12. doi:10.1023/A:1022353731579

Gevensleben, H., Holl, B., Albrecht, B., Schlamp, D., Kratz, O., Studer, P., & Heinrich, H. (2009). Distinct EEG effects related to neurofeedback training in children with ADHD: A randomized controlled trial. *International Journal of Psychophysiology, 74*(2), 149-157. doi:10.1016/j.ijpsycho.2009.08.005

Gevensleben, H., Kleemeyer, M., Rothenberger, L. G., Studer, P., Flaig-Röhr, A., Moll, G. H., & Heinrich, H. (2014). Neurofeedback in ADHD: Further pieces of the puzzle. *Brain Topography, 27*(1), 20-32. doi:10.1007/s10548-013-0285-y

Giddens, A. (1991). *Modernity and Self-Identity: Self and Society in the LateModern Age*. Stanford, CA: Stanford University Press.

Gossop, M., Stewart, D., Browne, N., & Marsden, J. (2002). Factors associated with abstinence, lapse or relapse to heroin use after residential treatment: Protective effect of coping responses. *Addiction, 97*(10), 1259-1267. doi:10.1046/j.1360-0443.2002.00227.x

Gottfredson, M. R., & Hirschi, T. (1990). *A general theory of crime* Stanford University Press.

Gruzelier, J., Hardman, E., Wild, J., & Zaman, R. (1999). Learned control of slow potential interhemispheric asymmetry in schizophrenia. *International Journal of Psychophysiology, 34*(3), 341-348. doi:10.1016/S0167-8760(99)00091-4

Gruzelier, J., Egner, T., & Vernon, D. (2006). Validating the efficacy of neurofeedback for optimising performance.

Progress in Brain Research, 159, 421-431. doi:10.1016/S0079-6123(06)59027-2
Gunkelman, J. D., & Johnstone, J. (2005). Neurofeedback and the brain. *Journal of Adult Development, 12*(2-3), 93-98. doi:10.1007/s10804-005-7024-x
Gullo, M. J., & Dawe, S. (2008). Impulsivity and adolescent substance use: Rashly dismissed as 'all-bad?'. *Neuroscience and Biobehavioral Reviews, 32*(8), 1507-1518. doi:10.1016/j.neubiorev.2008.06.003
Halligan, P. W., & David, A. S. (2001). Cognitive neuropsychiatry: Towards a scientific psychopathology. *Nature Reviews neuroscience, 2*(3), 209-215. doi:10.1038/35058586
Hammer, E. M., Halder, S., Blankertz, B., Sannelli, C., Dickhaus, T., Kleih, S., & Kübler, A. (2012). Psychological predictors of SMR-BCI performance. *Biological Psychology, 89*(1), 80-86. doi:10.1016/j.biopsycho.2011.09.006
Hammond, D. C., Bodenhamer-Davis, G., Gluck, G., Stokes, D., Harper, S. H., Trudeau, D., & Kirk, L. (2011). Standards of practice for neurofeedback and neurotherapy: A position paper of the international society for neurofeedback & research. *Journal of Neurotherapy, 15*(1), 54-64. doi:10.1080/10874208.2010.545760
Hanslmayr, S., Sauseng, P., Doppelmayr, M., Schabus, M., & Klimesch, W. (2005). Increasing individual upper alpha power by neurofeedback improves cognitive performance in human subjects. *Applied Psychophysiology and Biofeedback, 30*(1), 1-10. doi:10.1007/s10484-005-2169-8
Hare, R. D. (2003). *Manual for the Revised Psychopathy Checklist*. Toronto, Canada: Multi-Health Systems.
Hawkins, J. D., Catalano, R. F., & Miller, J. Y. (1992). Risk and protective factors for alcohol and other drug problems in adolescence and early adulthood: Implications for substance abuse prevention. *Psychological Bulletin, 112*(1), 64-105. doi:10.1037/0033-2909.112.1.64
Heatherton, T. F., & Wagner, D. D. (2011). Cognitive neuroscience of self-regulation failure. *Trends in Cognitive Sciences, 15*(3), 132-139. doi:10.1016/j.tics.2010.12.005
Heinrich, H., Gevensleben, H., Freisleder, F. J., Moll, G. H., & Rothenberger, A. (2004). Training of slow cortical potentials in attention-deficit/hyperactivity disorder: Evidence for positive behavioral and neurophysiological effects. *Biological Psychiatry, 55*(7), 772-775. doi:10.1016/j.biopsych.2003.11.013
Hentges, R. F., Shaw, D. S., & Wang, M. (2017). Early childhood parenting and child impulsivity as precursors to aggression, substance use, and risky sexual behavior in adolescence and early adulthood. *Development and Psychopathology,* doi:10.1017/S0954579417001596
Herbert, H., & Jasper, M.D. (1958). Committee on Methods of Clinical Examination in Electroencephalography. Report of the Committee on Methods of Clinical Examination in Electroencephalography. *Electroencephalography and Clinical Neurophysiology, 10*(2), 370-375. doi:10.1016/0013-4694(58)90053-1
Hermens, D. F., Kohn, M. R., Clarke, S. D., Gordon, E., & Williams, L. M. (2005). Sex differences in adolescent ADHD: Findings from concurrent EEG and EDA. *Clinical Neurophysiology, 116*(6), 1455-1463. doi:10.1016/j.clinph.2005.02.012
Higgins, J. P. T. & Green, S. (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.handbook.cochrane.org
Hodgins, S., Lapalme, M., & Toupin, J. (1999). Criminal activities and substance use of patients with major affective disorders and schizophrenia: A 2-year follow-up. *Journal of Affective Disorders, 55*(2-3), 187-202. doi:10.1016/S0165-0327(99)00045-2
Horner, R. H., Carr, E. G., Halle, J., McGee, G., Odom, S., & Wolery, M. (2005). The use of single-subject research to identify evidence-based practice in special education. *Exceptional Children, 71*(2), 165-179. doi:10.1177/001440290507100203
Horrell, T., El-Baz, A., Baruth, J., Tasman, A., Sokhadze, G., Stewart, C., & Sokhadze, E. (2010). Neurofeedback effects on evoked and induced EEG gamma band reactivity to drug-related cues in cocaine addiction. *Journal of Neurotherapy, 14*(3), 195-216. doi:10.1080/10874208.2010.501498
Horsfall, J., Cleary, M., Hunt, G. E., & Walter, G. (2009). Psychosocial treatments for people with co–occurring severe mental illnesses and substance use disorders (dual diagnosis): A review of empirical evidence. *Harvard Review of Psychiatry, 17*(1), 24-34. doi:10.1080/10673220902724599
Horvath, A. O., & Symonds, B. D. (1991). Relation between working alliance and outcome in psychotherapy: A meta-analysis. *Journal of Counseling Psychology, 38*(2), 139-149. doi:10.1037/0022-0167.38.2.139
Howard, M. O., Kivlahan, D., & Walker, R. D. (1997). Cloninger's tridimensional theory of personality and psychopathology: Applications to substance use disorders. *Journal of Studies on Alcohol, 58*(1), 48-66. doi:10.15288/jsa.1997.58.48

Hyun, J., Baik, M. J., & Kang, U. G. (2011). Effects of psychotropic drugs on quantitative EEG among patients with schizophrenia-spectrum disorders. *Clinical Psychopharmacology and Neuroscience, 9*(2), 78-85. doi:10.9758/cpn.2011.9.2.78

Imperatori, C., Della Marca, G., Amoroso, N., Maestoso, G., Valenti, E. M., Massullo, C., & Farina, B. (2017). Alpha/theta neurofeedback increases mentalization and default mode network connectivity in a non-clinical sample. *Brain Topography, 30*(6), 822-831. doi:10.1007/s10548-017-0593-8

Janssen, T. W. P., Bink, M., Weeda, W. D., Geladé, K., van Mourik, R., Maras, A., & Oosterlaan, J. (2017). Learning curves of theta/beta neurofeedback in children with ADHD. *European Child & Adolescent Psychiatry, 26*(5), 573-582. doi:10.1007/s00787-016-0920-8

Jentsch, J. D., & Taylor, J. R. (1999). Impulsivity resulting from frontostriatal dysfunction in drug abuse: Implications for the control of behavior by reward-related stimuli. *Psychopharmacology, 146*(4), 373-390. doi:10.1007/PL00005483

Jentsch, J. D., Ashenhurst, J. R., Cervantes, M. C., James, A. S., Groman, S. M., & Pennington, Z. T. (2014). Dissecting Impulsivity and its Relationship to Drug Addictions. *Annals of the New York Academy of Science, 1327*, 1-26. doi:10.1111/nyas.12388

Johnson, M. L., & Bodenhamer-Davis, E. (2009). QEEG-based protocol selection: A study oflevel of agreement on sites, sequences, and rationales among a group of experienced QEEG-based neurofeedback practitioners. *Journal of Neurotherapy, 13*(1), 41-66. doi:10.1080/10874200802668416

Joos, L., Goudriaan, A. E., Schmaal, L., de Witte, N. A. J., Van, d. B., Sabbe, B. G. C., & Dom, G. (2013). The relationship between impulsivity and craving in alcohol dependent patients. *Psychopharmacology, 226*(2), 273-283. doi:10.1007/s00213-012-2905-8

Jutai, J. W., & Hare, R. D. (1983). Psychopathy and selective attention during performance of a complex perceptual-motor task. *Psychophysiology, 20*(2), 146-151. doi:10.1111/j.1469-8986.1983.tb03280.x

Kamperman, A. M., Henrichs, J., Bogaerts, S., Lesaffre, E. M., Wierdsma, A. I., Ghauharali, R. R., et al. (2014). Criminal victimisation in people with severe mental illness: a multi-site prevalence and incidence survey in the Netherlands. *PLoS One, 9*(3):e91029. doi:10.1371/journal.pone.0091029

Keith, J. R., Rapgay, L., Theodore, D., Schwartz, J. M., & Ross, J. L. (2015). An assessment of an automated EEG biofeedback system for attention deficits in a substance use disorders residential treatment setting. *Psychology of Addictive Behaviors, 29*(1), 17-25. doi:10.1037/adb0000016

Konicar, L., Veit, R., Eisenbarth, H., Barth, B., Tonin, P., Strehl, U., & Birbaumer, N. (2015). Brain self-regulation in criminal psychopaths. *Scientific reports, 5*, 9426.

Kropotov, J. D., Grin-Yatsenko, V., Ponomarev, V. A., Chutko, L. S., Yakovenko, E. A., & Nikishena, I. S. (2005). ERPs correlates of EEG relative beta training in ADHD children. *International Journal of Psychophysiology, 55*(1), 23-34. doi:10.1016/j.ijpsycho.2004.05.011

Kübler, A., Neumann, N., Wilhelm, B., Hinterberger, T., & Birbaumer, N. (2004). Predictability of brain-computer communication. *Journal of Psychophysiology, 18*(2-3), 121-129. doi:10.1027/0269-8803.18.23.121

Kulacaoglu, F., & Kose, S. (2018). Singing under the impulsiveness: Impulsivity in psychiatric disorders. *Psychiatry and Clinical Psychopharmacology, 28*(2), 205-210. doi:10.1080/24750573.2017.1410329

Lackner, N., Unterrainer, H., Skliris, D., Wood, G., Wallner-Lieberman, S. J., Neuper, C., &Gruzelier, J. H. (2016). The Effectiveness of Visual Short-Time Neurofeedback on Brain Activity and Clinical Characteristics in Alcohol Use Disorders: Practical Issues and Results. *Clinical EEG and Neuroscience, 47*(3), 188-195. doi:10.1177/1550059415605686

Lang, P. J., & Twentyman, C. T. (1976). Learning to control heart rate: Effects of varying incentive and criterion of success on task performance. *Psychophysiology, 13*(5), 378-385. doi:10.1111/j.1469-8986.1976.tb00848.x

Ledgerwood, D. M., & Petry, N. M. (2010). Subtyping pathological gamblers based on impulsivity, depression, and anxiety. *Psychology of Addictive Behaviors, 24*(4), 680-688. doi:10.1037/a0019906

Leins, U., Goth, G., Hinterberger, T., Klinger, C., Rumpf, N., & Strehl, U. (2007). Neurofeedback for children with ADHD: A comparison of SCP and Theta/Beta protocols. *Applied Psychophysiology and Biofeedback, 32*(2), 73-88. doi:10.1007/s10484-007-9031-0

Lijffijt, M., & Barratt, E. S. Persoonlijke evaluatie : BIS-11. 2005. URL:http://www.impulsivity.org/measurement/bis11_Dutch [accessed 2016-09-26] [WebCite Cache ID 6ko0yHKwE]

Liechti, M. D., Maurizio, S., Heinrich, H., Jäncke, L., Meier, L., Steinhausen, H. C., Walitza, S., Drechsler, R., & Brandeis, D. (2012). First clinical trial of tomographic neurofeedback in attention- deficit/hyperactivity

disorder: Evaluation of voluntary cortical control. *Clinical Neurophysiology, 123*(10), 1989-2005. doi: 10.1016/j.clinph.2012.03.016

Linden, M., Habib, T., & Radojevic, V. (1996). A controlled study of the effects of EEG biofeedback on cognition and behavior of children with attention deficit disorder and learning disabilities. *Biofeedback & Self Regulation, 21*(1), 35-49. doi:10.1007/BF02214148

Longabaugh, R., & Morgenstern, J. (1999). Cognitive-behavioral coping-skills therapy for alcohol dependence: Current status and future directions. *Alcohol Research & Health, 23*(2), 78-85.

Loree, A. M., Lundahl, L. H., & Ledgerwood, D. M. (2015). Impulsivity as a predictor of treatment outcome in substance use disorders: Review and synthesis. *Drug and Alcohol Review, 34*(2), 119-134. doi:10.1111/dar.12132

Lubar, J. F., & Shouse, M. N. (1976). EEG and behavioral changes in a hyperkinetic child concurrent with training of the Sensorimotor Rhythm (SMR). A preliminary report. *Biofeedback and Self-Regulation, 1*(3), 293-306.

Lubar, J. F., Swartwood, M. O., Swartwood, J. N., & O'Donnell, P. H. (1995). Evaluation of the effectiveness of EEG neurofeedback training for ADHD in a clinical setting as measured by changes in TOVA scores, behavioral ratings, and WISC- R performance. *Biofeedback & Self Regulation, 20*(1), 83-99. doi:10.1007/BF01712768

Lyne, J., O'Donoghue, B., Roche, E., Renwick, L., Cannon, M., & Clarke, M. (2017). Negative symptoms of psychosis: A life course approach and implications for prevention and treatment. *Early Intervention in Psychiatry,* doi:10.1111/eip.12501

Lyvers, M. (2000). 'Loss of control' in alcoholism and drug addiction: A neuroscientific interpretation. *Experimental and Clinical Psychopharmacology, 8*(2), 225-249. doi:10.1037/1064-1297.8.2.225

Macdonald, S., Erickson, P., Wells, S., Hathaway, A., & Pakula, B. (2008). Predicting violence among cocaine, cannabis, and alcohol treatment clients. *Addictive Behaviors, 33*(1), 201-205. doi:10.1016/j.addbeh.2007.07.002

Machielsen, M., Beduin, A. S., Dekker, N., Kahn, R. S., Linszen, D. H., van Os, J., & Myin-Germeys, I. (2012). Differences in craving for cannabis between schizophrenia patients using risperidone, olanzapine or clozapine. *Journal of Psychopharmacology, 26*(1), 189-195. doi:10.1177/0269881111408957

Madden, G. J., Petry, N. M., Badger, G. J., & Bickel, W. K. (1997). Impulsive and self-control choices in opioid-dependent patients and non-drug-using control patients: Drug and monetary rewards. *Experimental and Clinical Psychopharmacology, 5*(3), 256-262. doi:10.1037/1064-1297.5.3.256

Magill, M., & Ray, L. A. (2009). Cognitive-behavioral treatment with adult alcohol and illicit drug users: A meta-analysis of randomized controlled trials. *Journal of Studies on Alcohol and Drugs, 70*(4), 516-527. doi:10.15288/jsad.2009.70.516

Mann, C. A., Lubar, J. F., Zimmerman, A. W., Miller, C. A., & Muenchen, R.A. (1992). Quantitative analysis of EEG in boys with attention-deficit hyperactivity disorder: controlled study with clinical implications. *Pediatric Neurology, 8*(1), 30-36.

MATLAB R2012b release. (2012). Natick: The Mathworks Inc.

Marissen, M. A. E., Franken, I. H. A., Blanken, P., Van, D. B., & Hendriks, V. M. (2005). Cue exposure therapy for opiate dependent clients. *Journal of Substance use, 10*(2-3), 97-105. doi:10.1080/14659805123313440075

Martin, G., & Johnson, C. L. (2005). The boys totem town neurofeedback project: A pilot study of EEG biofeedback with incarcerated juvenile felons. *Journal of Neurotherapy, 9*(3), 71-86. doi:10.1300/J184v09n03_05

Mayer, K., Wyckoff, S. N., Schulz, U., & Strehl, U. (2012). Neurofeedback for adult attention-deficit/hyperactivity disorder: Investigation of slow cortical potential neurofeedback-Preliminary results. *Journal of Neurotherapy, 16*(1), 37-45. doi:10.1080/10874208.2012.650113

Mayer, K., Blume, F., Wyckoff, S. N., Brokmeier, L. L., & Strehl, U. (2016). Neurofeedback of slow cortical potentials as a treatment for adults with attention deficit-/Hyperactivity disorder. *Clinical Neurophysiology, 127*(2), 1374-1386. doi:10.1016/j.clinph.2015.11.013

Merrin, E. L., & Floyd, T. C. (1992). Negative symptoms and EEG alpha activity in schizophrenic patients. *Schizophrenia Research, 8*(1), 11-20. doi:10.1016/0920-9964(92)90056-B

Moeller, F. G., Dougherty, D. M., Barratt, E. S., Schmitz, J. M., Swann, A. C., & Grabowski, J. (2001). The impact of impulsivity on cocaine use and retention in treatment. *Journal of Substance Abuse Treatment, 21*(4), 193-198. doi:10.1016/S0740-5472(01)00202-1

Moeller, S. J., & Paulus, M. P. (2018). Toward biomarkers of the addicted human brain: Using neuroimaging to predict relapse and sustained abstinence in substance use disorder. *Progress in Neuro-Psychopharmacology & Biological Psychiatry, 80*, 143-154. doi:10.1016/j.pnpbp.2017.03.003

Mohammadi, R. M., Malmir, N., Khaleghi, A., & Aminiorani, M. (2015). Comparison of Sensorimotor Rhythm (SMR) and Beta Training on Selective Attention and Symptoms in Children with attention deficit/hyperactivity Disorder (ADHD): A trend report. *Iranian Journal of Psychiatry, 10*(3), 165-174.

Monastra, V. J., Lubar, J. F., Linden, M., VanDeusen, P., Green, G., Wing, W., & Fenger, T. N. (1999). Assessing attention deficit hyperactivity disorder via quantitative electroencephalography: An initial validation study. *Neuropsychology, 13*(3), 424-433. doi:10.1037/0894-4105.13.3.424

Monastra, V. J., Monastra, D. M., & George, S. (2002). The effects of stimulant therapy, EEG biofeedback, and parenting style on the primary symptoms of attention-deficit/hyperactivity disorder. *Applied Psychophysiology and Biofeedback, 27*(4), 231-249. doi:10.1023/A:1021018700609

Monastra, V. J., Lynn, S., Linden, M., Lubar, J. F., Gruzelier, J., & LaVaque, T. J. (2005). Electroencephalographic biofeedback in the treatment of attention-Deficit/Hyperactivity disorder. *Applied Psychophysiology and Biofeedback, 30*(2), 95-114. doi:10.1007/s10484-005-4305-x

Moreno-García, I., Delgado-Pardoa, G., de Reya, C. C., Meneres-Sanchoa, S., & Servera-Barceló, M. (2015). Neurofeedback, pharmacological treatment and behavioral therapy in hyperactivity: Multilevel analysis of treatment effects on electroencephalography. *International Journal of Clinical and Health Psychology, 15*(3), 217-225. doi:10.1016/j.ijchp.2015.04.003

Morgan, D. L., & Morgan, R. K. (2001). Single-participant research design: Bringing science to managed care. *American Psychologist, 56*(2), 119-127. doi:10.1037/0003-066X.56.2.119

Nan, W., Wan, F., Chang, L., Pun, S. H., Vai, M. I., & Rosa, A. (2017). An exploratory study of intensive neurofeedback training for schizophrenia. *Behavioural Neurology, 2017* doi:10.1155/2017/6914216

Neumann, N., & Birbaumer, N. (2003). Predictors of successful self control during brain-computer communication. *Journal of Neurology, Neurosurgery & Psychiatry, 74*(8), 1117-1121. doi:10.1136/jnnp.74.8.1117

Nielsen, D. A., Ho, A., Bahl, A., Varma, P., Kellogg, S., Borg, L., & Kreek, M. J. (2012). Former heroin addicts with or without a history of cocaine dependence are more impulsive than controls. *Drug and Alcohol Dependence, 124*(1-2), 113-120. doi:10.1016/j.drugalcdep.2011.12.022

Nijboer, F., Furdea, A., Gunst, I., Mellinger, J., McFarland, D. J., Birbaumer, N. & Kübler, A. (2008). An auditory brain-computer interface (BCI). *Journal of Neuroscience Methods, 167*(1), 43-50. doi: 10.1016/j.jneumeth.2007.02.009

Nijboer, F., Birbaumer, N., & Kübler, A. (2010). The influence of psychological state and motivation on brain-computer interface performance in patients with amyotrophic lateral sclerosis- a longitudinal study. *Frontiers in Human Neuroscience, 4*, 55. doi: 10.3389/fnins.2010.00055

O'Brien, K., & Daffern, M. (2017). An exploration of responsivity among violent offenders: Predicting access to treatment, treatment engagement and programme completion. *Psychiatry, Psychology and Law, 24*(2), 259-277. doi:10.1080/13218719.2016.1230923

Ogloff, J. R., Wong, S., & Greenwood, A. (1990). Treating criminal psychopaths in a therapeutic community program. *Behavioral Sciences & the Law, 8*(2), 181-190. doi:10.1002/bsl.2370080210

Paim Kessler, F. H., Terra, M. B., Faller, S., Stolf, A. R., Peuker, A. C., Benzano, D., & Pechansky, F. (2012). Crack users show high rates of antisocial personality disorder, engagement in illegal activities and other psychosocial problems. *The American Journal on Addictions, 21*(4), 370-380. doi:10.1111/j.1521-0391.2012.00245.x

Palijan, T. Ž., Radeljak, S., Kovac, M., & Kovacevic, D. (2010). Relationship between comorbidity and violence risk assesment in forensic psychiatry-The implicaton of neuroimaging studies. *Psychiatria Danubina, 22*(2), 253-256.

Palmer, E. J., & Humphries, L. M. (2016). Differences between completers and non-completers of offending behaviour programmes: Impulsivity, social problem-solving, and criminal thinking. *Legal and Criminological Psychology, 21*(2), 407-416. doi:10.1111/lcrp.12089

Parker, R. I., & Vannest, K. (2009). An improved effect size for single-case research: Nonoverlap of all pairs. *Behavior Therapy, 40*(4), 357-367. doi:10.1016/j.beth.2008.10.006

Patrick, C. J., Bernat, E. M., Malone, S. M., Iacono, W. G., Krueger, R. F., & Mcgue, M. (2006). P300 amplitude as an indicator of externalizing in adolescent males. *Psychophysiology, 43*(1), 84-92. doi:10.1111/j.1469-8986.2006.00376.x

Patton, J. H., Stanford, M. S., & Barratt, E. S. (1995). Factor structure of the Barratt impulsiveness scale. *Journal of Clinical Psychology, 51*(6), 768-774. doi:10.1002/1097-4679(199511)51:6<768::AID-JCLP2270510607>3.0.CO;2-1

Pearson, F. S., & Lipton, D. S. (1999). A meta-analytic review of the effectiveness of corrections-based treatments for drug abuse. *The Prison Journal, 79*(4), 384-410. doi:10.1177/0032885599079004003

Peniston, E. G., & Kulkosky, P. J. (1991). Alpha-theta brainwave neuro-feedback therapy for vietnam veterans with combat-related post-traumatic stress disorder. *Medical Psychotherapy: An International Journal, 4*, 47-60.

Perry, J. L., & Carroll, M. E. (2008). The role of impulsive behavior in drug abuse. *Psychopharmacology, 200*(1), 1-26. doi:10.1007/s00213-008-1173-0

Pfurtscheller, G., & Lopes, d. S. (1999). Event-related EEG/MEG synchronization and desynchronization: Basic principles. *Clinical Neurophysiology, 110*(11), 1842-1857. doi:10.1016/S1388-2457(99)00141-8

Pfurtscheller, G., Brunner, C., Schlogl, A., & Lopes da Silva, F.H. (2006). Mu rhythm(de)synchronization and EEG single-trial classification of different motorimagery tasks. *Neuroimage, 31*(1), 153-159. doi:10.1016/j.neuroimage.2005.12.003

Pompili, E., Carlone, C., Silvestrini, C., & Nicolò, G. (2017). Focus on aggressive behaviour in mental illness. *Rivista Di Psichiatria, 52*(5), 175-179.

Quirk, D. A. (1995). Composite biofeedback conditioning and dangerous offenders: III. *Journal of Neurotherapy, 1*(2), 44-54. doi:10.1080/10874208.2012.10491665

Raine, A., Venables, P. H., & Williams, M. (1990). Relationships between N1, P300, and contingent negative variation recorded at age 15 and criminal behavior at age 24. *Psychophysiology, 27*(5), 567-574. doi:10.1111/j.1469-8986.1990.tb01978.x

Reddy, L. F., Lee, J., Davis, M. C., Altshuler, L., Glahn, D. C., Miklowitz, D. J., & Green, M. F. (2014). Impulsivity and risk taking in bipolar disorder and schizophrenia. *Neuropsychopharmacology, 39*(2), 456-463. doi:10.1038/npp.2013.218

Reichert, J. L., Kober, S. E., Neuper, C., & Wood, G. (2015). Resting-state sensorimotor rhythm (SMR) power predicts the ability to up-regulate SMR in an EEG-instrumental conditioning paradigm. *Clinical Neurophysiology, 126*(11), 2068-2077. doi:10.1016/j.clinph.2014.09.032

Reyes, A. C., & Amador, A. A. (2009). Qualitative and quantitative EEG abnormalities in violent offenders with antisocial personality disorder. *Journal of Forensic and Legal Medicine, 16*, 59-63. doi:10.1016/j.jflm.2008.08.001

Rizvi, S. L., & Nock, M. K. (2008). Single-case experimental designs for the evaluation of treatments for self-injurious and suicidal behaviors. *Suicide and Life-Threatening Behavior, 38*(5), 498-510. doi:10.1521/suli.2008.38.5.498

Rogala, J., Jurewicz, K., Paluch, K., Kublik, E., Cetnarski, R., & Wróbel, A. (2016). The do's and don'ts of neurofeedback training: A review of the controlled studies using healthy adults. *Frontiers in Human Neuroscience, 10*

Roozen, H. G., van, d. K., van Marle, H. J., & Franken, I. H. A. (2011). The impact of craving and impulsivity on aggression in detoxified cocaine-dependent patients. *Journal of Substance Abuse Treatment, 40*(4), 414-418. doi:10.1016/j.jsat.2010.12.003

Ros, T., Moseley, M. J., Bloom, P. A., Benjamin, L., Parkinson, L. A., & Gruzelier, J. H. (2009). Optimizing microsurgical skills with EEG neurofeedback. *BMC Neuroscience, 10* doi:10.1186/1471-2202-10-87

Rossiter, T. R., & La Vaque, T. J. (1995). A comparison of EEG biofeedback and psychostimulants in treating attention deficit/hyperactivity disorders. *Journal of Neurotherapy, 1*(1), 48-59. doi:10.1300/J184v01n01_07

Saletu, B., Anderer, P., Saletu-Zyhlarz, G. M. (2006). EEG topography and tomography (LORETA) in the classification and evaluation of the pharmacodynamics of psychotropic drugs. Clinical EEG and Neuroscience, 37(2), 66-80. doi:10.1177/155005940603700205

Samuels, J. (2011). Personality disorders: Epidemiology and public health issues. *International Review of Psychiatry, 23*(3), 223-233. doi:10.3109/09540261.2011.588200

Schneider, F., Rockstroh, B., Heimann, H., Lutzenberger, W., Mattes, R., Elbert, T., & Bartels, M. (1992). Self-regulation of slow cortical potentials in psychiatric patients: Schizophrenia. *Biofeedback & Self Regulation, 17*(4), 277-292. doi:10.1007/BF01000051

Schönenberg, M., Wiedemann, E., Schneidt, A., Scheeff, J., Logemann, A., Keune, P. M., & Hautzinger, M. (2017). Neurofeedback, sham neurofeedback, and cognitive-behavioural group therapy in adults with attention-deficit hyperactivity disorder: A triple-blind, randomised, controlled trial. *The Lancet Psychiatry, 4*(9), 673-684. doi:10.1016/S2215-0366(17)30291-2

Schuringa, E., Spreen, M., & Bogaerts, S. (2014). Inter-rater and test-retest reliability, internal consistency, and factorial structure of the instrument for forensic treatment evaluation. *Journal of Forensic Psychology Practice, 14*(2), 127-144. doi:10.1080/15228932.2014.897536

Schuringa, E., Heininga, V. E., Spreen, M. & Bogaerts, S. (2018). Concurrent and Predictive Validity of the Instrument for Forensic Treatment Evaluation (IFTE): From Risk Assessment to Routine, Multidisciplinary Treatment Evaluation. International Journal of Offender Therapy and Comparative Criminology, 62(5): 1281-1299. doi:10.1177/0306624X16676100

Scott, W. C., Kaiser, D., Othmer, S., & Sideroff, S. I. (2005). Effects of an EEG biofeedback protocol on a mixed substance abusing population. *The American Journal of Drug and Alcohol Abuse, 31*(3), 455-469. doi:10.1081/ADA-200056807

Siever, L. J., & Rosell, D. R. (2016). The neurobiology of violence. In K. D. Warburton, & S. M. Stahl (Eds.), (pp. 104-135). New York, NY: Cambridge University Press.

Simpson, A. I., Grimbos, T., Chan, C., & Penney, S. R. (2015). Developmental typologies of serious mental illness and violence: Evidence from a forensic psychiatric setting. *Australian and New Zealand Journal of Psychiatry, 49*(11), 1048-1059. doi:10.1177/0004867415587745

Small, J. G., Milstein, V., Sharpley, P. H., Klapper, M., & Small, I. F. (1984). Electroencephalographic findings in relation to diagnostic constructs in psychiatry. *Biological Psychiatry, 19*(4), 471-487.

Smith, P. N., & Sams, M. W. (2005). Neurofeedback with juvenile offenders: A pilot study in the use of QEEG-based and analog-based remedial neurofeedback training. *Journal of Neurotherapy, 9*(3), 87-99. doi:10.1300/J184v09n03_06

Snyder, S. M., & Hall, J.R. (2006). A meta-analysis of quantitative EEG power associated with attention-deficit hyperactivity disorder. *Journal of Clinical Neurophysiology, 23*(5), 440-455. doi:10.1097/01.wnp.0000221363.12503.78

Sokhadze, T. M., Cannon, R. L., & Trudeau, D. L. (2008). EEG biofeedback as a treatment for substance use disorders: Review, rating of efficacy and recommendations for further research. *Journal of Neurotherapy, 12*(1), 5-43. doi:10.1080/10874200802219855

Sokhadze, E., Stewart, C., Tasman, A., Daniels, R., & Trudeau, D. (2011). Review of rationale for neurofeedback application in adolescent substance abusers with comorbid disruptive behavioral disorders. *Journal of Neurotherapy, 15*(3), 232-261. doi:10.1080/10874208.2011.595298

Solanas, A., Manolov, R., & Onghena, P. (2010). Estimating slope and level change in N = 1 designs. *Behavior Modification, 34*(3), 195-218. doi:10.1177/0145445510363306

Spreen, M., Brand, E., ter Horst, P., & Bogaerts, S. (2014). Handleiding HKT-R [Manual of theHKT-R]. Groningen, The Netherlands: Stichting FPC Dr. S. van Mesdag.

. Stacy, A. W., & Wiers, R. W. (2010). Implicit cognition and addiction: A tool for explaining paradoxical behavior. *Annual Review of Clinical Psychology, 6*, 551-575. doi:10.1146/annurev.clinpsy.121208.131444

Stenberg, G. (1992). Personality and the EEG: Arousal and emotional arousability. *Personality and Individual Differences, 13*(10), 1097-1113. doi:10.1016/0191-8869(92)90025-K

Sterman, M. B. (1996). Physiological origins and functional correlates of EEG rhythmic activities: Implications for self-regulation. *Biofeedback & Self Regulation, 21*(1), 3-33. doi:10.1007/BF02214147

Stevens, L., Verdejo-García, A., Goudriaan, A. E., Roeyers, H., Dom, G., & Vanderplasschen, W. (2014). Impulsivity as a vulnerability factor for poor addiction treatment outcomes: A review of neurocognitive findings among individuals with substance use disorders. *Journal of Substance Abuse Treatment, 47*(1), 58-72. doi:10.1016/j.jsat.2014.01.008

Strehl, U., Leins, U., Goth, G., Klinger, C., Hinterberger, T., & Bierbaumer, N. (2006). Self-regulation of slow cortical potentials: A new treatment for children with attention-deficit/hyperactivity disorders. *Pediatrics, 118*(5), e1530-1540. doi: 10.1542/peds.2005-2478

Surmeli, T., Ertem, A., Eralp, E., & Kos, I. A. (2012). Schizophrenia and the Efficacy of qEEG-Guided Neurofeedback Treatment: A Clinical Case Series. *Clinical EEG and Neuroscience, 43*(2), 133-144. doi: 10.1177/1550059411429531

Swann, A. C., Bjork, J. M., Moeller, F. G., & Dougherty, D. M. (2002). Two models of impulsivity: Relationship to personality traits and psychopathology. *Biological Psychiatry, 51*(12), 988-994. doi:10.1016/S0006-3223(01)01357-9

Swann, A. C., Lijffijt, M., Lane, S. D., Steinberg, J. L., & Moeller, F. G. (2009). Trait impulsivity and response

inhibition in antisocial personality disorder. *Journal of Psychiatric Research, 43*(12), 1057-1063. doi:10.1016/j.jpsychires.2009.03.003

Swanson, J. W., Swartz, M. S., Essock, S. M., Osher, F. C., Wagner, H. R., Goodman, L. A., & Meador, K. G. (2002). The social-environmental context of violent behavior in persons treated for severe mental illness. *American Journal of Public Health, 92*(9), 1523-1531. doi:10.2105/AJPH.92.9.1523

Tanahashi Y. (1988). Electroencephalographic studies of borderline personality disorder. *Juntendo Medical Journal, 34*(2), 207-219.

Task Force on Promotion and Dissemination of Psychological Procedures, Division of Clinical Psychology, American Psychiatric Association. (1995). Training in dissemination of empirically-validated psychological treatments: Report and recommendations. *The clinical Psychologist, 48*(1), 3-23.

Tomko, R. L., Bountress, K. E., & Gray, K. M. (2016). Personalizing substance use treatment based on pre-treatment impulsivity and sensation seeking: A review. *Drug and Alcohol Dependence, 167*, 1-7. doi:10.1016/j.drugalcdep.2016.07.022

Tomko, R. L., Solhan, M. B., Carpenter, R. W., Brown, W. C., Jahng, S., Wood, P. K., & Trull, T. J. (2014). Measuring impulsivity in daily life: The momentary impulsivity scale. *Psychological Assessment, 26*(2), 339-349. doi:10.1037/a0035083

Trimbos-instituut, stuurgroep multidisciplinaire Richtlijnontwikkeling. (2008). *Richtlijn Dubbele Diagnose: Dubbele diagnose, dubbele hulp. Richtlijn voor diagnostiek en behandeling, versie 1.0.* Ontwikkelcentrum Kwaliteit en Innovatie van Zorg, in opdracht van GGZ Nederland - project Resultaten Scoren.

Trudeau, D. L. (2005). Applicability of brain wave biofeedback to substance use disorder in adolescents. *Child and Adolescent Psychiatric Clinics of North America, 14*(1), 125-136. doi:10.1016/j.chc.2004.07.006

Tziortzis, D., Mahoney, J. J. I., II, Kalechstein, A. D., Newton, T. F., & Garza, D. L. (2011). The relationship between impulsivity and craving in cocaine- and methamphetamine-dependent volunteers. *Pharmacology, Biochemistry and Behavior, 98*(2), 196-202. doi:10.1016/j.pbb.2010.12.022

Van der Veeken, F. C., Lucieer, J., & Bogaerts, S. (2016). Routine Outcome Monitoring and Clinical Decision-Making in Forensic Psychiatry Based on the Instrument for Forensic Treatment Evaluation. *PloS One, 12,* 11(8), e0160787.

Van Doren, J., Heinrich, H., Bezold, M., Reuter, N., Kratz, O., Horndasch, S., & Studer, P. (2017). Theta/beta neurofeedback in children with ADHD: Feasibility of a short-term setting and plasticity effects. *International Journal of Psychophysiology, 112*, 80-88. doi:10.1016/j.ijpsycho.2016.11.004

van Marle, Hjalmar J. C. (2002). The Dutch entrustment act (TBS): Its principles and innovations. *The International Journal of Forensic Mental Health, 1*(1), 83-92. doi:10.1080/14999013.2002.10471163

Van Nieuwenhuizen, C., Bogaerts, S., Ruijter, E., Bonges, I., & Coppens, M. (2011). *Profiling TBS-treatment: a structured cases analysis*. [TBS-behandeling geprofileerd -een gestructureerde casussenanalyse]. Wetenschappelijk Onderzoek- en Documentatiecentrum (WODC) The Netherlands: Ministry of Justice.

van Nimwegen, L. J., de Haan, L., van Beveren, Nico J. M., van, d. H., van, d. B., & Linszen, D. (2008). Effect of olanzapine and risperidone on subjective well-being and craving for cannabis in patients with schizophrenia or related disorders: A double-blind randomized controlled trial. *The Canadian Journal of Psychiatry / La Revue Canadienne De Psychiatrie, 53*(6), 400-405.

van Outsem, R. (2011). The applicability of neurofeedback in forensic psychotherapy: A literature review. *Journal of Forensic Psychiatry & Psychology, 22*(2), 223-242. doi:10.1080/14789949.2010.528012

Van Yperen, T., Veerman, & J.W., Bijl, B. (2017). *Zicht op effectiviteit. Handboek voor resultaatgerichte ontwikkeling van interventies in de jeugdsector* [Effectivity in perspective]. The Netherlands. Lemniscaat.

Vandevelde, S., Broekaert, E., Schuyten, G., & Van Hove, G. (2005). Intellectual abilities and motivation toward substance abuse treatment in drug-involved offenders: A pilot study in the belgian criminal justice system. *International Journal of Offender Therapy and Comparative Criminology, 49*(3), 277-297. doi:10.1177/0306624X04270779

Vassileva, J., Gonzalez, R., Bechara, A., Martin, E. M. (2007). Are all drug addicts impulsive? Effects of antisociality and extent of multidrug use on cognitive and motor impulsivity. *Addictive Behaviors, 32*(12), 3071-3076. doi:10.1016/j.addbeh.2007.04.017

Velotti, P., Garofalo, C., D'Aguanno, M., Petrocchi, C., Popolo, R., Salvatore, G., & Dimaggio, G. (2016). Mindfulness moderates the relationship between aggression and antisocial personality disorder traits: Preliminary investigation with an offender sample. *Comprehensive Psychiatry, 64*, 38-45. doi:10.1016/j.

comppsych.2015.08.004
Verdejo-García, A., Lawrence, A. J., & Clark, L. (2008). Impulsivity as a vulnerability marker for substance-use disorders: Review of findings from high-risk research, problem gamblers and genetic association studies. *Neuroscience and Biobehavioral Reviews, 32*(4), 777-810. doi:10.1016/j.neubiorev.2007.11.003
Vigilant, L. G. (2008). 'I am still suffering': The dilemma of multiple recoveries in the lives of methadone maintenance patients. *Sociological Spectrum, 28*(3), 278-298. doi:10.1080/02732170801898455
Volavka, J. (1990). Aggression, electroencephalography, and evoked potentials: A critical review. *Neuropsychiatry, Neuropsychology, & Behavioral Neurology, 3*(4), 249-259.
Volkow, N. D., Fowler, J. S., & Wang, G.J. (2003). The addicted human brain: insights from imaging studies. *Journal of Clinical Investigation, 111*, 1444-51. doi:10.1172/JCI18533
Weber, E., Köberl, A., Frank, S., & Doppelmayr, M. (2011). Predicting successful learning of SMR neurofeedback in healthy participants: Methodological considerations. *Applied Psychophysiology and Biofeedback, 36*(1), 37-45. doi:10.1007/s10484-010-9142-x
Weddington, W. W., Brown, B. S., Haertzen, C. A., Cone, E. J., Dax, E. M., Herning, R. I., & Michaelson, B. S. (1990). Changes in mood, craving, and sleep during short-term abstinence reported by male cocaine addicts: A controlled, residential study. *Archives of General Psychiatry, 47*(9), 861-868. doi:10.1001/archpsyc.1990.01810210069010
Welsh, W. N., Zajac, G., & Bucklen, K. B. (2014). For whom does prison-based drug treatment work? Results from a randomized experiment. *Journal of Experimental Criminology, 10*(2), 151-177. doi:10.1007/s11292-013-9194-z
Wiers, R. W., Ames, S. L., Hoffmann, W., Krank, M. & Stacey, A. W. (2010). Impulsivity, impulsive and reflective processes and the development of alcohol use and misuse in adolescents and young adults. *Frontiers in Psychology, 1*: 44. doi:10.3389/fpsyg.2010.00144
Wilens, T. E. (2004). Impact of ADHD and its treatment on substance abuse in adults. *The Journal of Clinical Psychiatry, 65*, 38-45.
Witte, M., Kober, S. E., Ninaus, M., Neuper, C., & Wood, G. (2013). Control beliefs can predict the ability to up-regulate sensorimotor rhythm during neurofeedback training. *Frontiers in Human Neuroscience, 7*
Woicik, K., Van der Lem, Sijtsema, J. J., & Bogaerts, S. (2017). Treatment no-show in forensic outpatients with ADHD. *Criminal Behaviour and Mental Health, 27*(1), 76-88. doi:10.1002/cbm.1989
Wyrwicka, W., & Sterman, M. B. (1968). Instrumental conditioning of sensorimotor cortex EEG spindles in the waking cat. *Physiology & Behavior, 3*(5), 703-707. doi:10.1016/0031-9384(68)90139-X
Zoefel, B., Huster, R. J., & Herrmann, C. S. (2011). Neurofeedback training of the upper alpha frequency band in EEG improves cognitive performance. *Neuroimage, 54*(2), 1427-1431. doi:10.1016/j.neuroimage.2010.08.078
Zuberer, A., Brandeis, D., & Drechsler, R. (2015). Are treatment effects of neurofeedback training in children with ADHD related to the successful regulation of brain activity? A review on the learning of regulation of brain activity and a contribution to the discussion on specificity. *Frontiers in Human Neuroscience, 9*. doi:10.3389/fnhum.2015.00135

Summary

This study is set in the FPC Dr. S. van Mesdag, a forensic psychiatric center (FPC) in Groningen, The Netherlands. Patients in this maximum security treatment facility are male forensic psychiatric patients with at least one mental disorder according to DMS-IV-TR (APA, 2000). Next to other mental disorders, about 70% of patients are diagnosed with substance abuse problems. Patients are receiving compulsory treatment by order of the state after committing a violent crime with a minimum penalty of at least four years according to Dutch jurisdiction (called Terbeschikkingstelling, or TBS; Van Marle, 2002). Due to mental illness, these patients were held only partially responsible for the crime they committed. The aim of the treatment is to reduce clinical symptoms that are considered high-risk for reoffending, and to integrate patients back into society by the means of stepwise furlough and expansion of liberties.

Background

Individuals with mental illness tend to exhibit inadequate coping mechanisms in response to stressful situations. Their behavior is often times rash and impulsive and can, in some cases, lead to acting-out behavior with significant negative consequences in the long term, such as the use of violence and committing criminal acts (Samuels, 2011; Pompili, Carlone, Silvestrini, & Nicole, 2017). Patients within a forensic psychiatric treatment facility usually present with an average of 3.5 diagnoses per patient (Van Nieuwenhuizen et al., 2011). Most common disorders are SUD, schizophrenia, attention-deficit/hyperactivity disorder (ADHD), impulse control disorders, and cluster B personality disorders, such as antisocial, borderline or narcissistic personality disorder (Schuringa, Heininga, Spreen, & Bogaerts, 2018; Simpson, Grimbos, Chan, & Penny, 2015). In order to treat these disorders, a broad range of treatment forms is applied, such as cognitive behavioral therapy, schema-focussed therapy and/ or non-verbal therapy. A complicating factor for effective treatment and compliance is the presence of complex comorbid problems such as high levels of impulsivity and substance use disorder (SUD). Impulsivity can be defined as a dysfunctional personality trait, resulting in a tendency for an individual to display behavior that is performed with little or inadequate forethought and little consideration for consequences of the own behavior (Evenden, 1999; Verdejo-Garcia, Lawrence, & Clark, 2008). For disorders high in impulsivity, increased prevalence of SUD is rather common (e.g. Loree et al., 2015). High levels of impulsivity are strongly associated with the development, maintenance and relapse in substance abuse and addiction (Hawinks, Catalano, & Miller, 1992; Charney, Zikos, & Gill, 2010) When moving from recreational to compulsive drug use, the use of an addictive substance is continued despite the negative consequences of prolonged drug abuse. Poor response control is associated with rapidly escalating drug use, where control over drug intake is lost and drug use starts to become compulsive (Perry & Carroll, 2008). Highly impulsive patients also tend to experience symptoms of withdrawal more seriously than less impulsive patients, as they report higher scores of craving for substances than patients with lower impulsivity scores (Joos et al., 2013), making them even more prone for relapse. Addictive substances may also increase impulsivity levels, as a structural state of reduced inhibitory control due to substance abuse leads to long-lasting neurocognitive and neurophysiological changes (Perry & Carroll, 2008). Once individuals seek treatment for substance abuse problems, treatment success is seriously hampered by high level of impulsivity (e.g., Charney, Zikos, & Gill, 2010; Van der Veeken, Lucieer, & Bogaerts, 2016). For forensic psychiatric patients especially, the maintenance of substance abuse poses risk for treatment failure. Drug abuse is a strong predictor of violent behavior, and

subsequent violent criminal recidivism (Duke, Smith, Oberleitner, Westphal, & McKee, 2018; MacDonald, Erickson, Wells, Hathaway, & Pakula, 2008).

Neurofeedback is an intervention that uses real-time EEG measurements and displays information about these EEG measurements back to the participant, allowing them to not only see but also change their brain electrical activity over time (Sokhadze, Stewart, Tasman, Daniels, & Trudeau, 2011). By principles of operant conditioning, participants learn to reinforce or inhibit specific frequencies of the EEG-activity (Scott, Kaiser, Othmer, & Sideroff, 2005) and thereby normalize abnormal EEG states, which in turn aims at changing abnormal psychological states (Gunckelman & Johnstone, 2005). Sensors are placed on the scalp and moment-to-moment information about brain activity is fed back to the participant (Hammond et al., 2011). Several studies have shown neurofeedback to be a promising intervention for various disorders, ranging from SUD to attention deficit hyperactivity disorder (ADHD) (Sokhadze et al., 2011). For the reduction of high levels of impulsivity, neurofeedback protocols typically focus on the reduction of slow wave activity such as theta, and enhancement of faster activity such as beta or SMR. Elevated theta activity has been consistently linked with higher levels of impulsivity across various subject populations (e.g., Bresnahan & Barry, 2002; Hermens, Kohn, Clarke, Gordon, & Williams, 2005; Stenberg, 1992). Increased SMR activity is seen when humans try to inhibit a motor response, and neurofeedback training where the SMR activity has been up-trained has been found to facilitate thalamic inhibitory mechanisms.

Neurofeedback is in its basics non-verbal and relies on the principles of operant condition, making it a suitable treatment intervention for a wide range of patient populations. Still, to date neurofeedback is hardly used in the forensic psychiatric domain. A possible reason for this could be the lack of guidelines that indicate how many sessions are needed to reach desired effects, or which patients are most likely to benefit from the training in terms of reduction of clinical symptoms.

This dissertation set out to investigate the efficacy of a theta/SMR neurofeedback intervention as an alternative for standard treatment of forensic psychiatric patients who suffer from disorders characterized by heightened levels of impulsivity, as well as comorbid substance use disorder.

Systematic review of the literature

In order to investigate to what extent neurofeedback training has been applied in disorders most commonly found in forensic psychiatric patients, **chapter 2** presents a systematic review of previous studies on neurofeedback training for mental disorders commonly found in forensic psychiatric patients. The article discusses the implications of these studies for the applicability of neurofeedback training in forensic psychiatric patient populations. Although the search was conducted for numerous disorders, as well as for behavior commonly associated with high levels of impulsivity, the search resulted in only 10 studies that fulfilled the inclusion criteria. The included studies were all related to neurofeedback training in patients with ADHD, schizophrenia, SUD and psychopathy. No studies could be identified that applied neurofeedback for cluster B personality disorders, or impulsive behavior often found in forensic psychiatric patients, such as violence.

For the studies included, EEG-training protocols as well as number of training sessions varied greatly. Number of applied training sessions ranged from 10 to 33 sessions. Also, results on patients' ability for EEG-learning varied greatly between studies and patient populations.

Changes in behavioral outcome measures post-training ranged from no improvements to significant symptom reduction. Uncontrolled studies (Arns, Drinkenburg, & Kenemans, 2012; Mayer, Wyckoff, Schulz, & Strehl, 2012) found improvements in impulsivity, but no superiority of neurofeedback training to TAU could be observed when a sham controlled, blinded approach was employed (Schönenberg et al., 2017). Based on these findings, it can be concluded that more research is needed to be able to make inferences about which protocol or how many training sessions should result in the most beneficial effects for forensic psychiatric patients.

Study Protocol

In order to investigate the effects of neurofeedback training on forensic psychiatric patient, several studies were performed. **Chapter 3** describes the study protocol for a randomized controlled trial (RCT) design with a n-of-1 clinical series. All patients in this study had at least one diagnosis of SUD, as well as comorbid Axis I and/or II disorders according to DSM-IV-TR (American Psychiatric Association, 2000). For both the RCT and the clinical case series, primary outcome variables were the degree of impulsivity, as well as levels of craving, and changes in resting-state EEG pattern. The RCT compared the effects of 20 sessions of theta/SMR neurofeedback training to a control group who received TAU only. In this RCT, impulsivity was assessed with the Barratt Impulsivity Scale (BIS-11) and a cued Go/No-Go task. Furthermore, levels of craving were assessed with a modified form of the Desire for Alcohol Questionnaire, as well as actual drug use by collecting results on urine and/or breathalyzer analysis.

To investigate interpersonal and individual differences between patients with regard to successful EEG-learning more deeply, a N-of-1 clinical case series was also employed. In the clinical case series, four patients in the control group of the RCT were randomly assigned to either eight sessions of real theta/SMR neurofeedback training or sham neurofeedback training. Comparing the effects of real theta/SMR neurofeedback training to sham neurofeedback training allows for investigating possible placebo effects of this intervention. An ABA design was employed, where a no-training baseline phase (A^1) was followed by a neurofeedback training phase (B), which was then followed again by a no-training follow-up phase (A^2). During the course of the study, the same questionnaires that were assessed during the RCT were also assessed.

Neurofeedback learning

Chapter 4 reports the results for a subset of the patients who participated in neurofeedback training. It was investigated whether forensic psychiatric patients diagnosed with SUD were able to learn to regulate neurophysiological activity through a theta/SMR neurofeedback and to what extent magnitude changes in these frequency bands were related to changes in levels of impulsivity. Criteria for qualifying patients as responders were established and scores on impulsivity measures and changes in level of craving over time were assessed. Patients were categorized as a 'neurofeedback-responder' when they showed both a successful upregulation of SMR magnitude and a successful downregulation of theta magnitude during at least 11 out of 19 sessions, as well as an average magnitude increase/decrease in the desired direction of 8% or higher by the end of the training. These criteria were chosen based on the proposed protocol described in Weber, Köberl, Frank, and Doppelmayer (2011). Results indicated that only four out of 19 patients (21%) were able to achieve successful regulation of both frequency bands by these criteria. Patients found it more difficult to regulate theta frequency than SMR frequency as

evidence by the fact that 63% of patients managed to successfully increase the SMR magnitude, whereas only 37% of patients managed to decrease theta magnitude. As can be seen in **chapter 4**, Spearman's rho correlations between number of times patients successfully achieved up- or downregulation in the desired direction and height of average increase or decrease in the frequency band was significant at the $\alpha < 0.01$ level in a single frequency (either theta or SMR), as well as for the number of times SMR and theta were successfully regulated simultaneously. Results also indicated that impulsivity levels, as well as levels of craving were significantly lower post-training for all patients, regardless of whether they had been qualified as neurofeedback responders or not. However, subsequent analyses showed that the ability to consistently train frequency bands in the desired direction was not related to scores on impulsivity measures post-training. The variance in levels of craving post-training could partially be explained by whether patients could be categorized as responders, as this was related to the increase in SMR frequency but not to a decrease in theta frequency.

Effects of neurofeedback training

In **chapter 5**, the results of the RCT were presented. The RCT was conducted according to the design described in the study protocol in **chapter 3**. Patients eligible for participation according to the inclusion criteria were randomly assigned to either the neurofeedback training group or the treatment as usual (TAU) group. 42 patients completed all post-treatment measurements, of which 21 patients participated in the control group and 21 patients in the neurofeedback training group. Results of the RCT showed that patients who received neurofeedback training managed to increase SMR activity over the course of training, but failed to decrease theta activity. Levels of drug craving showed a significant effect for Time, but not for Time x Group. Results for changes in drug use and number of commission errors post-treatment were not significant. Therefore, theta/SMR neurofeedback training was not superior to TAU with regards to behavioral improvements for the examined patient group.

Chapter 6 describes the results of a sham-controlled series of clinical case studies, where two cases employed a SMR neurofeedback protocol and two cases employed sham neurofeedback. Self-report level of impulsivity and craving were assessed.

Results of this clinical case series indicated that both patients in the real neurofeedback condition responded differently to the training in terms of change in outcome measures, with one of the patients receiving real theta/SMR neurofeedback benefitting more from the training than the other patient. This patient showed a significant decrease in impulsivity as measured with the BIS-11. Results regarding levels of craving as measured with the DAQ-SF showed that this patient also had a significant reduction in DAQ-SF scores when comparing baseline phase A^1 with follow-up phase A^2. He also showed partial signs of neurofeedback learning, as he was able to increase SMR frequency over the course of training, however, this effect did not remain significant when controlling for autocorrelation. Theta magnitude did not change.

Neurofeedback as a suitable treatment for forensic psychiatric patients?

The results of this dissertation show that for forensic psychiatric patients with SUD, it is difficult to learn the principles of neurofeedback training. In studies with healthy participants or patients with less severe disorders, training two EEG-training parameters at the same time seems manageable, but these EEG-learning patterns seem to be incongruent with EEG-learning

observed in the population that was investigated in the studies of this dissertation. It is possible that for patients with severe mental disorders, the patterns of EEG-learning are not congruent with patterns of learning in healthy subjects. It remains unclear why patients were more able to train their SMR magnitude than their theta magnitude. Possibly, EEG-learning might take different patterns to manifest than in other populations. EEG-learning might take more time to manifest, and may therefore require a higher number of sessions than the applied 20 sessions in the current RCT. However, performance in early sessions of neurofeedback training has been shown to predict performance in later sessions (e.g., Kübler, Neumann, Wilhelm, Hinterberger, & Birbaumer, 2004; Neumann & Bierbaumer, 2003; Weber et al., 2011). It therefore remains questionable whether more training sessions would have actually resulted in more EEG-learning in forensic psychiatric patients. Also, none of the patients was able to follow the training as originally scheduled, as training sessions twice a week were apparently too intensive for some patients. It is likely that more patients would have dropped out if more sessions and/or a more intense training schedule had been required. With regard to improvements on behavioral measures, the RCT showed that neurofeedback training was not more effective than TAU only. This may not be entirely unexpected as only a small proportion of patients were able to actually change their brain frequencies through the training. Since neurofeedback training is based on the hypothesis that changes at behavioral level are brought about by changes in EEG-frequencies, it seems obvious that no changes at behavioral level have been found.

Directions for future studies

This is one of the first studies to apply a neurofeedback intervention in a forensic psychiatric population with various disorders and comorbid SUD. This dissertation gives a first start for the application of the training in this population, and we hope that future research can build on the results described in this dissertation.

A necessary condition for the broad application of neurofeedback training is to investigate which patients are capable of actually learning the principles of the training. Future research should therefore focus on developing a method that can determine early on in the training whether a patient will be able to regulate his EEG-frequencies, and which patient will most likely not achieve successful regulation, even with more sessions. Given that forensic psychiatric patients are a very vulnerable patient population that is difficult to motivate for treatment as it is, it is of great importance to offer these patients treatment modalities that offer them the greatest chance of reduction of symptoms. Identifying interpersonal mechanisms, which determine which patients benefit most from this intervention, should therefore be a high priority.

In addition, it is necessary to further investigate whether successful regulation of brain frequencies will actually lead to changes at behavioral level. Possibly, the protocol used in this thesis is not effective for this patient population, but other protocols can bring about changes at behavior level. In doing so, it also needs to be examined how many sessions are needed to find effects, as well as how many and which frequencies generate the most improvements.

The recent revival of personalized medicine, in which the specific characteristics of individual patients are more closely considered in the treatments to be used, also gives hope for the further application of neurofeedback training, where individual differences determine which training protocols are used to what extent.

Zusammenfassung

Die Studien in dieser Dissertation sind im Forensisch Psychiatrischen Centrum Dr. S. van Mesdag in Groningen durchgeführt. In dieser Klinik befinden sich ungefähr 250 männliche Patienten mit einem Maßregelvollzug. Diese Personen haben alle eine Straftat begangen, wofür sie allerdings aufgrund einer psychischen Störung oder mangelnden Entwicklung der geistigen Fähigkeiten nur begrenzt schuldfähig befunden wurden. In diesen Fällen kann dem Straftäter ein Maßregelvollzug aufgelegt werden, bei dem er in einer entsprechenden Maßregelvollzugsklinik therapiert wird. *„Ohne Schuld handelt, wer bei Begehung der Tat wegen einer krankhaften seelischen Störung, wegen einer tiefgreifenden Bewusstseinsstörung oder wegen Schwachsinns oder einer schweren anderen seelischen Abartigkeit unfähig ist, das Unrecht der Tat einzusehen oder nach dieser Einsicht zu handeln"(***§20 StGB)**. Das Ziel eines Maßregelvollzugs besteht darin, Patienten auf ein Leben in Freiheit so vorzubereiten, dass sie keine weitere Straftaten begehen.
Diese Dissertation studiert die Auswirkungen eines Neurofeedback Trainings auf die Impulsivität und die Symptome von Suchterkrankung von diesen Patienten. Die Dissertation besteht aus mehreren Teilen, die in den folgenden Abschnitten näher erläutert werden.

Hintergrund
Menschen mit einer psychischen Störung haben oft unzureichende Bewältigungsmechanismen, mit denen sie auf stressige Situationen oder Ereignisse angemessen reagieren können. Ihr Verhalten ist oft spontan und unüberlegt und bezieht mögliche (negative) Konsequenzen nicht mit ein. Dies kann soweit führen, dass sie ein Verbrechen begehen.
Patienten, die mit einem Maßregelvollzug in einer Maßregelvollzugsklinik verbleiben, leiden häufig an einer Kombination mehrerer psychischen Störungen. Die häufigsten Störungen sind Persönlichkeitsstörungen, Störungen im Schizophrenie-Spektrum oder Suchterkrankungen. Um diese Störungen zu behandeln, gibt es verschiedene Therapiemethoden, die eingesetzt werden können, wie z. B. kognitive Verhaltenstherapie, medikamentöse Behandlungen und/oder Therapiemethoden wie zum Beispiel Ergotherapie. Die Behandlung von diesen Patienten erweist sich jedoch oft als langwieriger und mühsamer Prozess. Da die Behandlung in einem gesetzlich vorgeschriebenen Rahmen erfolgt, ist die Therapiemotivation dieser Patienten oft gering und es besteht die Möglichkeit, dass es innerhalb des Maßregelvollzugs zu aggressiven Vorfällen kommt.
Ein hoher Grad an Impulsivität ist ein häufiges Merkmal psychiatrischer Störungen. Impulsivität ist ein dysfunktionales Persönlichkeitsmerkmal, bei dem eine Person nicht länger in der Lage ist, die positiven, kurzfristigen Konsequenzen gegen die möglichen negativen längerfristigen Konsequenzen abzuwägen.
Impulsivität spielt auch eine wichtige Rolle bei der Entwicklung und Aufrechterhaltung von Suchtverhalten. Sehr impulsive Menschen haben ein größeres Risiko, eine Suchterkrankung zu entwickeln, die oft schon in der Pubertät angelegt wird. Hier kann ein Mangel an Impulskontrolle dazu führen, dass sie schneller die Kontrolle über den Gebrauch von Suchtmitteln verlieren und der Gebrauch hiervon auf lange Sicht zwanghaft wird. Es besteht hierbei oft eine Wechselwirkung zwischen einem bereits vorhandenen, erhöhten Grad an Impulsivität und der weiteren enthemmenden Wirkung von Suchtmitteln. Drogen und Suchtstoffe können zu strukturellen neurophysiologischen und neurokognitiven Veränderungen führen, die die Impulskontrolle noch weiter negativ beeinflussen.
Patienten haben durch ein hohes Maß an Impulsivität ein erhöhtes Risiko, die Therapie ihrer

Suchterkrankung vorzeitig zu beenden. Da eine unbehandelte Suchterkrankung das Risiko auf einen Rückfall in ein Strafverhalten erhöht, ist das Scheitern einer Suchtbehandlung für Patienten in einem Maßregelvollzug besonders riskant. Daher sind Therapiemethoden, die die Chance einer erfolgreichen Reduktion von Impulsivität und Drogenabhängigkeit erhöhen, von großer Bedeutung.

Was ist Neurofeedback Training?

Neurofeedback Training ist eine relativ neue Therapiemethode, die heutzutage häufig zur Behandlung von ADHS eingesetzt wird. Neurofeedback Training richtet sich auf das korrigieren von abnormale Gehirnfrequenzen. Diese abnormalen Gehirnfrequenzen unterliegen den Symptomen psychischer Störungen. Das Erhöhen oder Verringern bestimmter Gehirnfrequenzen kann die Symptome von psychischen Störungen reduzieren. Patienten lernen hierbei, ihre abnormalen Gehirnfrequenzen zu normalisieren, indem sie Computerspiele ansteuern, die ihre Gehirnaktivität widergeben.

Eine erhöhte Theta-Frequenz wird oft bei sehr impulsiven Menschen beobachtet. Darüber hinaus scheint eine Erhöhung der sensorimotor rhythm frequenz mit einer Verringerung der Motorimpulsivität verbunden zu sein. Um die Impulsivität zu reduzieren, werden darum häufig Neurofeedback Protokolle verwendet, die sich auf die Senkung der Thetafrequenz (3,5-7,5 Hz) und die Erhöhung der SMR frequenz (12-15 Hz) konzentrieren. Neurofeedback könnte eine geeignete Therapiemethode darstellen, um einen hohen Grad an Impulsivität bei forensisch psychiatrischen Patienten zu reduzieren und hierdurch möglicherweise auch suchtbezogenes Verhalten, wie etwa das Verlangen nach Drogen und die Einnahme von Drogen, zu reduzieren.

Neurofeedback wird jedoch heutzutage zur Therapierung von forensisch psychiatrischen Patienten sowohl in den Niederlanden als auch international noch nicht häufig eingesetzt. Der Grund dafür könnte darin liegen, dass es bisher keine klaren Richtlinien darüber gibt, wie viele Therapiesitzungen des Trainings benötigt werden, um die bestmögliche Wirkung des Trainings zu erzielen. Es ist außerdem unklar, welche Patienten am meisten von diesem Training profitieren können.

Systematische Aufarbeitung des Forschungsstands

Um zu untersuchen, inwieweit diese Therapiemethode bei den am häufigsten vorkommenden psychischen Störungen eingesetzt wird und welche Auswirkungen dies hatte auf Symptome der psychischen Erkrankungen, wurde in **Kapitel 2** eine systematische Aufarbeitung des Forschungsstands durchgeführt. Dies ergab, dass in forensischen Patientenzielgruppen kaum Effektstudien zu Neurofeedback Training durchgeführt wurden, die die möglichen Auswirkungen dieses Trainings auf psychische Störungen und damit verbundenes Problemverhalten, wie Aggression und/oder impulsives Verhalten, untersuchen. Es konnten nur Studien identifiziert werden, die die Auswirkungen des Trainings auf ungefähr vergleichbare Patientenzielgruppen untersucht haben. Die Literaturstudie ergab auch, dass die Anzahl der verwendeten Therapiesitzungen stark variiert zwischen den untersuchten Studien, sowie den gefundenen Effekten des Trainings. Einige der Studien zeigten eine Verbesserung der Symptome auf Verhaltensebene, andere Studien hingegen konnten keine eindeutige Wirkung des Trainings finden. In einem Teil der Studien wurde zudem untersucht, inwieweit Patienten die Prinzipien des Neurofeedback Trainings erlernen konnten. Hierzu wurde analysiert, ob und in welchem Ausmaß sich die Gehirnfrequenzen der Patienten nach

dem Training tatsächlich normalisierten. Auch hierzu waren die Ergebnisse zu divers um eindeutige Schlussfolgerungen zu ziehen, die für den Einsatz von Neurofeedback Training in einer forensisch psychiatrischen Zielgruppe genutzt werden könnten. Es ist daher notwendig, die Auswirkungen des Neurofeedback Trainings auf den Grad der Impulsivität und Drogenabhängigkeit in einer forensischen Patientenzielgruppe genauer zu untersuchen.

Study Protocol

Um die Auswirkungen des Neurofeedback Trainings in einer forensisch psychiatrischen Patientenzielgruppe zu untersuchen, wurden eine Reihe von Studien durchgeführt. **Kapitel 3** beschreibt den Aufbau eines randomized controlled trial (RCT) sowie den Aufbau von vier N = 1 Fallstudien. Für den RCT untersuchten wir die Effekte von 20 Sitzungen einer Theta/SMR Neurofeedback Therapie auf 21 männlichen Patienten mit verschiedenen Störungen und komorbider Suchterkrankung. Die Patienten in diesem RCT hatten alle in den letzten 24 Monaten einen Rückfall in Drogenkonsum. Ziel dieses RCT war es, den Grad der Impulsivität, sowie die Sucht nach Drogen und den tatsächlichen Konsum hiervon zu verringern.

Bei dem eingesetzten Neurofeedback Protokoll wurde die Thetafrequenz reduziert und die SMR-Frequenz erhöht. Um die Auswirkungen des Trainings zu erfassen, wurden diese Patienten mit 21 Patienten verglichen, die zur gleichen Zeit das reguläre Therapieprogramm absolvierten, aber kein Neurofeedback Training erhielten (treatment as usual, TAU).

Um zwischenmenschliche Unterschiede hinsichtlich des Neurofeedback Lernverhaltens genauer untersuchen zu können, wurden anschließend vier Fallstudien durchgeführt. In diesen Fallstudien wurden die Effekte eines Neurofeedback Trainings von 8 Sitzungen mit den Effekten eines Sham-Neurofeedback Trainings verglichen, in dem keine einzige Gehirnfrequenz strukturell trainiert wurde. Die teilnehmenden Patienten wussten nicht, in welche Trainingsgruppe sie eingeteilt wurden. In dieser Studie wurde ein ABA-Design eingesetzt, bei dem der Trainingsverlauf von Patienten in mehrere Phasen unterteilt wurde. In der ersten Phase (A) füllten Patienten lediglich Fragebögen zum Grad der Impulsivität und des Suchtverhaltens aus, wohingegen sie in der zweiten Phase (B) zusätzlich 8 Therapiesitzungen des Neurofeedback Trainings erhielten. Nach dieser Phase wurde Phase A wiederholt.

Sind forensich psychiatrische Patienten in der Lage, das Training zu erlernen?

Bevor die Auswirkungen des Neurofeedback Trainings untersucht werden konnten, war es uns allerdings wichtig zu erfahren, inwieweit Patienten aus der Neurofeedback Trainingsgruppe die Prinzipien des Trainings erlernen konnten. In **Kapitel 4** wird analysiert, inwiefern Patienten in der Lage waren, ihre Gehirnfrequenzen gezielt durch das Training zu regulieren. Hierzu wurde ein Teil der Zielgruppe von 19 Patienten untersucht. Um das Training als erfolgreich betrachten zu können, musste ein Patient zeigen, dass er sowohl seine Theta- als auch SMR-Frequenz in 11 von den 19 untersuchten Therapiesitzungen regulieren konnte. Darüber hinaus musste der Patient am Ende des Trainings eine Verbesserung der relevanten Frequenzen um 8% nachweisen.

Die Ergebnisse dieser Studie zeigen, dass das verwendete Neurofeedback Trainingsprotokoll bei 15 von 19 Patienten nicht zu den erwarteten Veränderungen der Gehirnfrequenzen geführt hat. Nur 21% der Patienten konnten alle Kriterien für eine erfolgreiche Therapie erfüllen. Weitere Analysen zeigten, dass es für Patienten leichter war, die SMR-Frequenz erfolgreich zu regulieren als die Thetafrequenz.

Darüber hinaus wurde untersucht, inwieweit die erfolgreiche Regulation der Frequenzbänder mit Verbesserungen der Symptome auf Verhaltensebene zusammenhängt. Dies zeigte, dass eine erfolgreiche Regulation von Frequenzbändern nicht mit Veränderungen des Grads der Impulsivität zusammenhängt. Eine Reduktion der Sucht nach Drogen hing nur mit der erfolgreichen Regulierung der SMR-Frequenz zusammen, jedoch nicht mit der Thetafrequenz.

Auswirkungen des Neurofeedback Trainings

Anschließend untersuchten wir in **Kapitel 5** die Auswirkungen des Neurofeedback Trainings für die gesamte Patientengruppe und verglichen diese mit den Patienten, die das Training nicht erhalten hatten. Es stellte sich heraus, dass Patienten aus der Neurofeedback Trainingsgruppe in der Lage waren, ihr SMR-Frequenzband durch das Training zu erhöhen, aber dass keine Veränderungen beobachtet werden konnten für die Theta-Frequenz.
Die Sucht nach Drogen nahm für alle Patienten ab, unabhängig davon, ob sie in die Trainingsgruppe eingeteilt wurden oder nicht. Es gab keine Veränderung, was den Grad der Impulsivität betraf. Das verwendete Neurofeedback Training war daher nicht effektiver als reguläre Therapiemethoden.

Fallstudien

Kapitel 6 beschreibt die Ergebnisse der Fallstudien. Diese Fallstudien zeigen, dass die Patienten, die das Theta/SMR Neurofeedback Training absolvierten, unterschiedlich auf das Training reagierten. Von den zwei teilnehmenden Patienten zeigte nur der erste Patient Verbesserungen im Hinblick auf den Grad der Impulsivität sowie auf das Suchtverhalten. Er konnte seine SMR-Frequenz während des Trainings erhöhen, allerdings nicht seine Thetafrequenz reduzieren. Der zweite teilnehmende Patient zeigte weder eine signifikanten Veränderung in der SMR- noch in der Thetafrequenzen nach dem Training. Darüber hinaus konnten keine signifikanten Effekte für Veränderungen des Impulsivitätsgrads und der Sucht nach Drogen gefunden werden. Für den Patienten, der das Sham Neurofeedback Training absolvierte, wurden keine Verbesserungen gefunden.

Neurofeedback als geeignete Therapiemethode für forensisch psychiatrische Patienten mit Substanzabhängigkeit?

Die Ergebnisse der verschiedenen Studien in dieser Dissertation zeigen, dass es für forensisch psychiatrische Patienten mit komorbider Suchterkrankung schwierig ist, Gehirnfrequenzen mittels Neurofeedback Training zu regulieren. In Studien mit gesunden Probanden scheint ein Neurofeedback Trainingsprotokoll, bei dem zwei Gehirnfrequenzen gleichzeitig trainiert werden, gut geeignet zu sein. Dies gilt auch für Studien, in denen Patienten an einer einzigen psychischen Störung leiden, statt wie in unserer Zielgruppe an verschiedenen Störungen. Das Lernverhalten scheint sich jedoch anders zu manifestieren in forensischen Zielgruppen mit mehreren psychischen Störungen. Möglicherweise ist es für forensisch psychiatrische Patienten zu schwierig, zwei Gehirnfrequenzen gleichzeitig zu trainieren. Es ist unklar, warum Patienten weniger Schwierigkeiten hatten, ihre SMR-Frequenz zu regulieren, als ihre Thetafrequenz. Eine mögliche Erklärung ist, dass Patienten mit 20 Therapiesitzungen nicht genug Zeit hatten zu lernen, ihre Gehirnfrequenzen und insbesondere ihre Thetafrequenz zu regulieren. Möglicherweise würde diese doch sehr spezielle Patientenzielgruppe von einer höheren Anzahl Therapiesitzungen profitieren. Jedoch haben Studien auch gezeigt, dass die Leistung der

Patienten zu Beginn des Trainings ein Prädiktor für die Leistung in späteren Sitzungen ist. Dies würde bedeuten, dass Patienten, denen es nicht gelungen ist, ihre Frequenzbänder innerhalb von 20 Sitzungen zu regulieren, dies wahrscheinlich auch in späteren Sitzungen nicht mehr gelernt hätten. Es ist allerdings fragwürdig, ob eine höhere Anzahl von Therapiesitzungen tatsächlich zu besseren Ergebnissen geführt hätte. Weitere Studien sind nötig, um eindeutigere Schlüsse ziehen zu können. Darüber hinaus war es für Patienten, die an dieser Studie teilnahmen, sehr schwierig, sich auf den vorgegebenen Trainingsplan von zwei Therapiesitzungen pro Woche festzulegen. Eine höhere Anzahl an Sitzungen hätte höchstwahrscheinlich zu einer höheren vorzeitigen Abbruchrate der Therapie geführt.

Empfehlungen für zukünftige Studien

Dies ist eine der ersten Studien, die Neurofeedback Training in einer forensisch psychiatrischen Zielgruppe mit verschiedenen, psychischen Erkrankungen und komorbider Suchterkrankung, untersucht. Diese Dissertation gibt einen ersten Anstoß für die Anwendung dieser Therapieform in dieser Patientengruppe und wir hoffen, dass zukünftige Studien auf den Ergebnissen dieser Arbeit aufbauen können.

Eine notwendige Voraussetzung für die breite Anwendung von Neurofeedback Training ist die Identifikation von den Patienten, die in der Lage sind, die Prinzipien des Trainings tatsächlich zu erlernen. Zukünftige Studien sollten sich daher darauf konzentrieren, eine Methode zu entwickeln, die schon in einem frühen Stadium der Therapiesitzungen feststellen kann, ob ein Patient in der Lage ist, seine Gehirnfrequenzen durch das Training zu regulieren. Da es sich bei forensisch psychiatrischen Patienten um eine sehr spezialistische Patientenzielgruppe handelt, die schwer für eine Behandlung zu motivieren ist, ist es von großer Bedeutung, diesen Patienten eine Therapieform anzubieten, die ihnen die größten Erfolgschancen bietet.

Die Identifizierung zwischenmenschlicher Mechanismen, die beeinflussen, welche Patienten am meisten von dieser Therapie profitieren, sollte daher große Priorität haben. Darüber hinaus ist es notwendig, weiter zu untersuchen, ob eine erfolgreiche Regulierung der Gehirnfrequenzen tatsächlich zu Veränderungen auf der Verhaltensebene führt.

Möglicherweise führt das in dieser Dissertation angewandte Protokoll für die untersuchte Patientengruppe nicht zu den gewünschten Ergebnissen, aber andere Protokolle können Veränderungen auf der Verhaltensebene bewirken. Es sollte in zukünftigen Studien auch untersucht werden, wie viele Therapiesitzungen nötig sind, um die bestmöglichen Ergebnissen zu erreichen, sowie wie viele und welche Frequenzbänder die meisten Verbesserungen zu Stande bringen. Die rezente Wiederbelebung von ‘personalized medicine’, bei der die spezifischen Eigenschaften einzelner Patienten in der Behandlungen stärker berücksichtigt werden, lässt auch auf eine Weiterentwicklung des Neurofeedback Trainings hoffen, bei dem individuelle Unterschiede darüber entscheiden, welche Trainingsprotokolle in welchem Umfang eingesetzt werden.

Dankwoord

Toen ik mijn masterscriptie in de Mesdag deed had ik me niet kunnen voorstellen dat dit uiteindelijk zou gaan resulteren in een promotie. Onderzoek doen in een bijzondere setting als de Mesdag was een ontzettend leerzaam en uitdagend proces, en ik ben heel blij dat ik deze kans heb mogen benutten.
Een proefschrift beginnen, en sterker nog, afronden is een lang en soms moeilijk proces. Dat dit boekje er ligt heb ik te danken aan een aantal mensen in mijn leven die veel te zelden horen hoe belangrijk ze voor me zijn. Zonder jullie had ik het niet kunnen doen.

Marinus, zonder jou was ik nooit aan deze proefschrift begonnen. Tijdens mijn master had je al een onverwoestbaar vertrouwen in een goede scriptie, en ook tijdens dit traject heb je dit onverwoestbaar vertrouwen op zo veel momenten laten blijken. Je onvoorwaardelijke steun, je eindeloze energie om "lekker te gaan spss-en", en al de vrije tijd die je hebt opgeofferd om aan een nieuwe analysemethode te sleutelen die mijn artikelen vooruit zou kunnen helpen, hebben mijn proefschrift gemaakt tot het boekje dat er nu ligt. Ik ben je erg dankbaar voor de kansen die je me hebt gegeven. Onze gezamenlijke tijd in de Mesdag samen zit erop, maar ik ga je missen!
Franc, zonder jouw komst bij dit project in 2012 was deze proefschrift nooit afgerond. Bedankt voor je bereidheid om tijd vrij te maken om een absolutly clueless promovenda op weg te helpen met de beginselen van EEG-afnames! Je was er op afstand bij betrokken, en toch altijd bereikbaar. Je nam er de tijd voor als dat nodig was en ik heb me altijd welkom gevoeld. Niemand heeft zo grondig naar artikelen gekeken als jij, en je commentaar was altijd waardevol. Daarnaast ben je ook gewoon een fijn mens en kon ik heel prettig met jou samenwerken. Ik wil je ontzettend bedanken voor alle hulp en steun!
Stefan, zonder jouw was deze proefschrift niet mogelijk geweest. Je was altijd op de achtergrond bezig om ervoor te zorgen dat dit project door kon gaan. Heel erg bedankt dat je me de deze kans hebt gegeven!

Grote dank gaat uit naar mijn **collega's van afdeling onderzoek (Marlies, Swanny, Martine, Erwin, Mariette en Harmke)**. Met jullie deelde ik de eerste jaren niet alleen een kamer, maar ook lief en leed. Jullie hebben allen op jullie eigen manier meegedacht met dit onderzoek, en niemand anders begreep zo goed hoe het is om onderzoek te doen in deze bijzondere setting. **Erwin**, the master of Excel, aan jou een bijzonder dank voor alle hulp met ingewikkelde spreadsheets, het opmaken van tabellen en figuren, en vooral voor het feit dat je me nooit het idee hebt gegeven dat het een ontzettend domme vraag was die ik daar stelde (al was het in de meeste gevallen natuurlijk wel zo). Ik waardeer het enorm dat jij na een tijd waarin we het niet altijd eens met elkaar waren diegene was die de eerste stap heeft genomen en dat je deur ook nu nog voor me open staat.
Harmke, naast collega ook lotgenoot, en veel belangrijker, maatje. Je had altijd wel opbeurende woorden, en je mantra 'Jij kunt dit' heeft me vele malen geholpen om toch weer aan het werk te gaan en een aantal zinnen op papier te zetten. En op de momenten dat het dan toch echt niet wou stond er altijd een drankje voor me klaar.
Mariette, in de laatste jaren een aantal keren per week mijn kamergenootje, en tegelijkertijd vraagbak voor alles wat met promoveren te maken heeft. Jij wist als geen ander hoe moeilijk het soms kon zijn, maar doordat ik via jou het proces van het schrijven EN het daadwekelijk afmaken van een proefschrift kon gaan volgen heeft me dat vaak gemotiveerd om weer bezig te gaan.

Sander, jij laat zien dat passie en bevlogenheid voor je werk ook na een aantal jaren niet hoeft af te nemen. Ik ben je erg dankbaar voor de kansen en verantwoordelijkheden die je me hebt toevertrouwt in de loop der jaren. Je deur stond altijd open om te sparren, en je warme en oprechte belangstelling voor je medemens maakt dat we veel gedeeld hebben. Daarnaast ben je een van de grappigste mensen die ik ken, en je gevoel voor humor heeft menig lange autorit en vrijdag middag een stuk leuker gemaakt.

Dank aan alle stagiaires (**Rick, Angela, Maureen, Ingrid**) die met hun onderzoek hebben meegewerkt aan dit project, draaiboeken hebben geschreven, data hebben verzameld, patiënten hebben geworven, diploma's hebben geknutseld… Dank!

Een hele grote dank gaat uit naar alle **patiënten** die hebben meegewerkt aan deze studie! Jullie zijn bereid geweest om mee te werken aan een behandeling waarvan de effecten nog ongewis zijn. Velen van jullie hebben deelgenomen in de hoop eindelijk af te kunnen komen van je verslaving, en ik hoop dat jullie op de een of andere manier iets aan dit project hebben gehad.

Bedankt aan alle **collega's uit de Mesdag** die hebben geholpen om patiënten te motiveren (en gemotiveerd te houden!) – zonder sociotherapeuten, behandelcoördinatoren en mentoren hadden we nooit zo veel patiënten kunnen overtuigen om mee te werken.

Mama, Papa, David, eigentlich müsst ihr ganz oben auf dieser Liste stehen, denn ohne euch wäre ich nicht wo ich jetzt bin. Ihr habt mich immer meinen eigenen Weg gehen lassen, und stand jederzeit am Wegesrand um mich anzumutigen und Erfolge zu feiern.

Gelukkig waren er gedurende de afgelopen jaren ook veel momenten dat ik even niet bezig was met promoveren. Ik heb altijd kunnen bouwen op mensen in mijn omgeving, die het leven een stuk leuker maken: **mijn paranimfen - Stephanie**, wat was ik blij toen je er bij kwam als promovenda om lief en leed mee te delen. We zaten vaak in hetzelfde schuitje, en het was ontzettend fijn om iemand te hebben die precies weet wat je bedoelt. Bedankt voor alle goede zorg, sushi-deliveries na een dag zwoegen, lieve kaartjes en idiote berichtjes. **Lejanne,** sinds een aantal jaren ben je een belangrijk mens in mijn leven en daar ben ik ontzettend blij mee. Mijn bestekla ook trouwens.
Lise, het was mooi om je ontwikkeling van stagiair tot st, abc en uiteindelijk Gz-psycholoog te mogen volgen. Van schuilen in de regen op Vlieland tot met zn drieën in een veels te kleine auto op weg naar weer een festival, ik hoop dat er nog vele mogen volgen. **Marit,** dank voor veel gezelligheid met de mannen en lieve berichtjes. **Sara**, für 20 (!!) Jahre. **Alessa,** für Geburtstagskuchen und schlagermotivationsvideos. It's a thing. **Mijn volleybalmaatjes**, die niet alleen op de donderdag avonden voor de nodige afleiding hebben gezorgd, maar waar ik ook heb geleerd om heel erg blij voor elkaar te zijn om soms hele kleine dingen ('Hij is wel over!!').

Maar als allerbelangrijkste, **Koos.** Bij jou thuis komen was iedere keer weer het allerleukste deel van mijn dag.