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Review of Rationale for Neurofeedback Application in Adolescent Substance Abusers with Comorbid Disruptive Behavioral Disorders

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REVIEW ARTICLE

REVIEW OF RATIONALE FOR NEUROFEEDBACK APPLICATION IN ADOLESCENT SUBSTANCE ABUSERS WITH COMORBID DISRUPTIVE BEHAVIORAL DISORDERS

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Neurofeedback is a type of operant conditioning in which an individual modifies the frequency, amplitude, or other characteristic of his or her own brain activity as measured by EEG. Neurofeedback-training-based neurotherapy is one of the potentially efficacious nonpharmacological treatment options for substance use disorders (SUD) in adults, but it is also a very promising as a treatment modality for adolescents, especially those with stimulant abuse and attention and conduct problems. There is practically no literature on the use of neurofeedback in adolescent drug abusers. Treatment of attention-deficit/ hyperactivity disorder (ADHD) with neurofeedback has already gained substantial empirical support in recent years. Short-term effects were shown to be comparable to those of stimulant medication at the behavioral and neuropsychological level, leading to significant decreases of inattention, hyperactivity, and impulsivity. In addition, neurofeedback results in concomitant improvement and normalizations of neurophysiological patterns assessed with EEG, event-related potentials (ERPs), and fMRI. Neurofeedback techniques may be of special interest for adolescent medicine because of the high comorbidity of SUD and ADHD in adolescents. ADHD is often comorbid with other disruptive behavioral disorders such as conduct disorder and oppositional defiant disorder. Techniques that combine classic ADHD neurofeedback approaches with behavioral addiction treatment hold special interest for adolescents with dual diagnosis. They are medication free and thus both minimize opportunities for prescribed medication misuse and diversions and are free of medication side effects. Furthermore, neurofeedback directly acts on the specific brain activity that are known to be altered in SUD and ADHD. By providing low-risk and medication-free therapy for both ADHD and SUD, neurofeedback is an option for practitioners reluctant to prescribe controlled substances to ADHD adolescents at risk for substance abuse.

CLINICAL CHARACTERISTICS OF SUD, ADHD, AND OTHER DISRUPTIVE BEHAVIORAL DISORDERS IN ADOLESCENTS

Alcohol and Drug Abuse in Youth: Prevalence and Psychiatric Comorbidities

Drug Abuse. The alcohol and other psychoactive substance use disorder (SUD) commonly referred to as "drug addiction" is a chronic, relapsing mental disorder. The high prevalence of drug and alcohol use, and the incidence of substance abuse in children and adolescents, has become a major public health concern in the United States. According to the Substance Abuse and Mental Health Services Administration (SAMHSA, 2007) report, about 28.2% of children and adolescents aged 12 to 20 reported drinking alcohol, and rates of reported illicit drug use was 17% among 16- to 17-year-olds and as high as 22.3% among 18- to 20-year-olds. More alarming, the rate of substance dependence or abuse in 12- to 17-year-olds has been reported to be as high as 8.0%. Despite a slight decrease in alcohol and drug abuse rates (as compared to previous years, e.g., 8.8% in 2004 reports), epidemiological statistics point to the widespread use of alcohol and illegal substances by underage persons in the United States, and SUD development in children and adolescents younger than 21 should be of public concern. The youth are exposed to drugs at early ages, especially in cities. For example, in the Louisville metro area since 2003, more than 2,500 youth have been assessed by Louisville Adolescent Network for Substance Abuse Treatment, and more than 70% were found to have started using substances between 10 and 14 years of age. The years of use ranged from 44% reporting 1 to 2 years of use to 28% reporting 3 to 4 years of use and 20% reporting 5+ years of use. Among those, 32% were already reporting dependence symptoms. In the Louisville metro area population, the following substance use profile was reported: 10% used alcohol, 46% marijuana, 1% crack/cocaine, 4% opioids, and 5% other drugs (Daniels & Laundenwich, 2007).

Comorbidities. Couwenbergh et al. (2006), in a review, analyzed the prevalence of comorbid psychiatric disorders in nontreated adolescents and young adults with SUD in the general population. The prevalence of comorbid psychiatric disorders varied from 61% to 88%. Externalizing disorders, especially attention-deficit/hyperactivity disorder (ADHD), conduct disorder (CD), and oppositional defiant disorder (ODD), were most consistently linked to SUD in treatment seeking male adolescents. Female adolescent drug abusers were distinguished by their high rate of comorbid internalizing disorders (Chan, Dennis, & Funk, 2008). Comparison with data from community and juvenile justice studies shows an ascending trend of comorbidity rates of externalizing disorders from community to clinical and finally to juvenile justice samples. It seems that young addicts with comorbid behavioral disorders are at higher risk of ending up in the juvenile justice system. Childhood behavioral problems are important risk factors for the development of SUD (Cadoret, Troughton, & O'Gorman, 1987; Horner & Scheibe, 1997; Simkin, 2002; Tarter et al., 2003; Tarter, Kirisci, Habeych, Reynolds, & Vanyukov, 2004). Kirisciet, Vanyukov, and Tarter (2005), in a long-term prospective investigation of 351 boys whose parents had either SUD or no adult psychiatric disorder, found out that behavioral disinhibition in childhood in conjunction with parental SUD places the child at a very high risk for SUD by age 22. It has been suggested that common genetic risk factors may underlie childhood behavioral disorders and adulthood alcohol and drug dependence (Bauer & Hesselbrock, 2001).

Attention-Deficit/Hyperactivity Disorder, Conduct Disorder, and Oppositional Defiant Disorder: Prevalence and Characterization of Behavioral Comorbidities

ADHD. ADHD is one of the most common psychiatric conditions of childhood affecting between 5 and 6% of school-age children (Clarke, Barry, McCarthy, & Selikowitz, 2001).

Some studies cite an even higher prevalence rate (up to 7.5%) among 6- to 17-year-olds (Graetz, Sawyer, Hazell, Arney, & Baghust, 2001), with the last decades seeing a fourfold increase in the number of children diagnosed with this disorder (Brownell & Yogendran, 2001). ADHD occurs more frequently in male children and adolescents than in females, with a ratio of approximately 3 to 1 (Hermens, Kohn, Clarke, Gordon, & Williams, 2005). The primary symptoms of ADHD are distractibility, impulsivity, and hyperactivity (American Psychiatric Association [APA], 2000). ADHD interferes with normal development and functioning and, if untreated, is a risk factor predisposing children to psychiatric and social pathology in later life. Even though controlled studies indicate that up to 80% of ADHD children have beneficiary clinical effects from stimulant medications (e.g., methylphenidate and dexamphetamine; Swanson et al., 1998; Swanson et al., 2001; Swanson et al., 2007), the majority of parents with an ADHD child either do not seek or discontinue treatment because of the fear of adverse medication effects (Monastra et al., 2005; Monastra, Monastra, & George, 2003). Reluctance of medication usage is a significant impediment to treatment, and therefore, development of nonpharmacological approaches of ADHD treatment is needed.

Other Disruptive Behavioral Disorders Comorbid with ADHD. The most common comorbid disorders in ADHD are disruptive behavioral disorders (DBD), with studies reporting that between 42% and 93% of children with ADHD have CD or ODD (J. Anderson, Williams, McGee, & Silva, 1987; Aron & Poldrack, 2005; Barry, Clarke, McCarthy, & Selikowitz, 2007; Biederman et al., 2006; Bird, Gould, & Staghezza, 1993; Clarke, Barry, McCarthy, & Selikowitz, 2002; Clarke, Barry, McCarthy, Selikowitz, & Brown, 2002; Pliszka, 1998). DBD (i.e., CD and ODD) are characterized by a recurring and persistent pattern of antisocial behavior involving the violation of others' rights and societal norms (Lahey, Loeber, Quay, Frick, & Grimm, 1992; Loeber, Burke, Lahey, Winters, & Zera, 2000; Pardini

& Fite, 2010; Pardini, Fite, & Moffitt, 2010). CD account for about half of all youth referrals for psychiatric services. Youth exhibiting various forms of CD victimize others, disrupt families, fail at school, commit crimes in the community, and often abuse alcohol and illicit drugs. These behavioral disorders inflict significant psychological, social, and economic costs on youth, families, and communities, as they incur costs of remedial education, law enforcement, heavy utilization of mental health services, property damage, vandalism, substance abuse, teen pregnancy, high rate of school dropout, and criminality (Prinz, 1998). CD symptoms emerged as the most robust predictor of future antisocial outcomes. However, ODD symptoms predicted later criminal charges, and CD symptoms were robustly associated with serious and persistent criminal behavior in boys. ADHD symptoms predicted increases in oppositional defiant behavior and conduct problems over time and were uniquely related to future academic difficulties. Both ADHD and ODD symptoms predicted social, externalizing, and internalizing problems in youth, especially in boys (Pardini & Fite, 2010).

Burke, Waldman, and Lahey (2010) analyzed predictive validity of CD and ODD diagnosis as defined by the *Diagnostic and Statistical Manual of Mental Disorders* (4th ed., text rev. [*DSM–IV–TR*]; APA, 2000) and the *International Statistical Classification of Disease and Related Health Problems* (10th rev.; World Health Organization, 1992) and showed that they predict both future psychopathology and enduring functional impairment. Furthermore, they reported findings generally supportive for the hierarchical developmental hypothesis in *DSM–IV–TR* that some children with ODD progress to childhood-onset CD and some youth with CD progress to antisocial personality disorder. Nonetheless, the authors found that ODD does not always progress to CD, particularly during adolescence. On the other hand, CD and ODD are relatively rare and often overlap with the ADHD (Mcardle, O'Brien, & Kolvin, 1995; Prinz, 1998; Schachar & Tannock, 1995). Although EEG studies have found consistent differences between children

with and without ADHD, attention deficit is often a highly comorbid disorder, being found in conjunction with CD or ODD (Jensen, Martin, & Cantwell, 1997).

Explanations of Behavioral Disorders and Substance Abuse Relationship in Adolescents

Behavioral Factors. There is substantial evidence to suggest that children and adolescents diagnosed with ADHD and comorbid disruptive behaviors are more likely to develop problems related to substance use than those without these comorbidities (Biederman et al., 1995; Biederman et al., 1997; Biederman et al., 2006; Gittleman, Mannuzza, Shenker, & Bonagura, 1985; Mannuzza et al., 1991; Mannuzza, Klein, Konig, & Giampino, 1989; Mannuzza, Klein, & Moulton, 2003). Furthermore, there is evidence to suggest that childhood ADHD increases the risk of substance use in adults even in the absence of other behavioral comorbidities (Biederman et al., 1995). Therefore, although behavioral problems may explain substance use in ADHD adolescents, ADHD may be a stronger predictor of substance use in adulthood. There have been proposed several explanatory behavioral models of this risk. So-called self-medication theory of addiction (Khantzian, 1985, 1997) may explain the ADHD–substance abuse relationship proposing that persistent ADHD symptoms may lead to impairments in academic, family, and social functioning, and these impairments in turn may cause a propensity to use alcohol or drugs to cope with functional deficits (Cyders & Smith, 2008; Kalbag & Levin, 2005). However, individuals with ADHD may be more likely to use any substance they may get rather than solely use only stimulant drugs that increase their ability to concentrate (e.g., cocaine, amphetamine). One of the important characteristics of adolescent drug users is that they belong to a so-called opportunistic users' category, because they do not have yet preferred substance choice formed as compared to adult drug addicts. Furthermore, high impulsivity and low behavior inhibition control typical for ADHD individuals may drive them to try a novel substance even

without thinking about the consequences. Very often, adolescent drug users with ADHD report that they tried drugs offered by their peers because of their impulsive behaviors rather than seeking relief from ADHD symptoms. One more possible behavioral explanation for the observed association between ADHD and substance use is that exposure to stimulants prescribed for ADHD treatment in children increases the likelihood that they will misuse substances in adulthood. This increased risk is thought to occur by the process of behavioral sensitization to medication and belief that, because a prescribed stimulant medication has been indicated for them, other stimulants drugs can be used without any risk of abuse (Kalbag & Levin, 2005). Adolescents represent a vulnerable group at heightened risk for experimentation with narcotic substances, and the early experimentation is known to be associated with higher rates of substance dependence development in adulthood (Schepis, Adinoff, & Rao, 2008). Identification of individual behavioral risk factors that influence initiation and escalation of alcohol and drug use in the adolescent population is an important task necessary to define directions and strategies for preventive efforts (Swadi, 1999).

Neurobiological Factors. There are as well several neurobiological factors involved in the etiology of adolescent addiction, and various neural and behavioral mechanisms are implicated in its development. Some of these neurobiological developmental factors such as normative immature frontal-limbic connections, immature frontal lobe development, lesser myelination and lesser pruning than in adults, lowered serotonergic function, and abnormal hypothalamic-pituitary-adrenal axis function are capable of predisposing adolescents to a heightened risk for SUD. Dysregulation of the dopamine transporter (genetic factor) has also been implicated in the pathophysiology of ADHD and result in overpresentation of substance abuse (Doyle et al., 2005; Winterer et al., 2003). Imbalance in the adolescent behavioral activation/inhibition system (Gray's BIS/BAS; Corr, 2002) may be related to the relative underdevelopment of frontal

inhibitory mechanisms. According to Schepis et al. (2008), these neurobiological liabilities may correspond and translate to behavioral impairments in decision making, keeping company with behaviorally deviant peers, and other externalizing behavior; these and other cognitive and behavioral traits converge with neurobiological factors to increase SUD risk. According to Steinberg (2007), adolescents' inclination to engage in risky behavior does not appear to be due only to behavioral immaturity signs (irrationality, delusions of invulnerability, or ignorance) but rather can be explained by developmental neuroscience perspectives. According to this view, the temporal gap between puberty, which impels adolescents toward thrill seeking ("sensation seeking"), and the slow maturation of the cognitive-control system, which regulates these impulses, makes adolescence a life period of heightened vulnerability for risky behavior including drug abuse (Doehnert, Brandies, Imhof, Drechsler, & Steinhausen, 2010; Durston & Konrad, 2007). A better understanding of adolescent neurobiology and behavioral specifics is a necessary step in the development of prevention and treatment interventions for adolescent substance abuse. Early identification and neurobiological theory-driven treatment of young people with substance misuse and comorbid mental health problems may alter the developmental trajectory leading to potentially serious consequences in this population at risk (Mirza & Mirza, 2008).

Emotional Factors. It has been shown that emotional abnormalities are typical for addicts at any age (Fukunishi, 1996; Wexler et al., 2001). Alexithymia, that is, state of deficiency in understanding, processing, or describing emotions, is highly prevalent among substance abusers (Brady, 1997; Bremner, Southwick, Darnell, & Charney, 1996; Fukunishi, 1996; Hestler, Dixon, & Garavan, 2006; Ouimette, Finney, & Moos, 1999). Addicted individuals could be affected by a dysfunction associated with changes in emotional reactivity to natural positive reinforcers (Aguilar de Arcos, Verdejo-Garcia, Peralta-Ramirez, Sanchez-Barrera, & Perez-Garcia, 2005; Gerra et al., 2003).

Sensitization to drugs (Robinson & Berridge, 2008), and counter adaptation is hypothesized to contribute to dysregulation of hedonic homeostasis and to observed brain reward system abnormalities according to the "allostasis" theory (Koob, 1999; Koob & Le Moal, 2001).

Anhedonia and dysphoric moods may occur as well in children and adolescents as individual psychological traits that make them vulnerable to experimentation with drugs. ADHD is also characterized by emotional disturbances such as mood lability, dysphoria, temper outbursts, and so on (APA, 2000). CD has even more extreme emotional deficiency manifestations. Adolescents with CD seem to have an inability to correctly "read" emotions of peers and instead will misunderstand the intentions of others, many times believing that people are threatening them or letting them down, when this is not really the case. They tend to react to these supposed threats or put downs in an aggressive manner without showing any feeling or remorse. They do not tolerate frustration well and often escalate negative emotions and moods.

In addition to attentional and cognitive impairment, there are disruptions in processing emotion and mood abnormalities in teenage individuals with ADHD (De Boo & Prins, 2007) and substance abuse, but little is known about the neural basis of these affective impairments. L. M. Williams et al. (2008), in a study on 51 unmedicated ADHD adolescents and 51 matched healthy controls, rated subjects both for depressed and anxious mood and for accuracy in identifying the facial expressions of basic emotion. It seems reasonable to pay more attention to affective abnormalities in SUD, ADHD, and other disruptive behavioral disorders and to examine disturbances in emotion recognition and processing in adolescents with dual diagnosis.

CURRENT STRATEGIES OF TREATMENT FOR ADHD AND SUBSTANCE ABUSE IN ADOLESCENTS

Treatment Approaches in ADHD and SUD

ADHD. Even though controlled studies indicate that ADHD children have positive

clinical outcome from stimulant medications (Biederman, 2003; Schubiner et al., 2002; Swanson et al., 2001; Swanson et al., 1998), the majority of parents with an ADHD are reluctant to seek pharmacological treatment or discontinue treatment due to the fear of side effects (Monastra et al., 2005). A decade ago, the results of a National Institute of Mental Health–sponsored trial, which compared several treatments in 579 children, were published (the "Multimodal Treatment of ADHD" [MTA] study; MTA Cooperative Group, 1999; Swanson et al., 2001). Although the medication and combination treatment groups showed the greatest improvement after 14 months of treatment, half of these effects had dissipated at 10 months after treatment, and at the 8 year follow-up there were no longer any differences found between the four groups (Molina et al., 2009; MTA Cooperative Group, 2004). This multicenter large-scale study clearly demonstrates a lack of long-term effects for stimulant medication, multicomponent behavior therapy, or multimodal treatment (Molina et al., 2009). These results clearly show that at present there is no treatment modality that has sufficient long-term efficacy for ADHD and that there is a need for new treatments with better long-term outcomes (Sherlin, Arns, Lubar, & Sokhadze, 2010).

SUD. Despite increased prevalence of SUD in adolescents, only about 10% of adolescents needing treatment actually enter treatment (SAMHSA, 2007), suggesting a sizable gap between needed treatment and available specialized services (Becker & Curry, 2008; Etheridge, Smith, Rounds-Bryant, & Hubbard, 2001; Franzer, 2005; Knudsen, 2009; Sussman, 2010). Adolescents seeking treatment often face barriers to treatment entry, such as strict admission policies, and limited availability of adolescent-only treatment programs. Although many existing adolescent drug abuse treatment programs have a positive effect on outcomes (J. Anderson et al., 1987; K. G. Anderson, Ramo, Cummins, & Brown, 2010; Brannigan, Schackman, Falco, & Millman, 2004; Hser, Grella et al., 2001; Hser, Hoffman, Grella, & Anglin, 2001), it is necessary to provide continuous care and follow-up to

address the high possibility of posttreatment relapse. Addressing these complex needs requires more advanced cognitive and behavioral assessment and behavioral treatment services delivered to youth. Despite some expansion in research on the development of more efficient interventions for substance-abusing adolescents (Deas & Thomas, 2001; Dennis, White, Titus, & Unsicker, 2006; P. D. Riggs & Jellinek, 1998), few studies have examined the quality of "treatment as usual" in community-based adolescent treatment programs, and even fewer have tried to develop new emerging treatment techniques. Data from our local Louisville Adolescent Network for Substance Abuse Treatment center (Daniels & Laundenwich, 2007) show that 74% of the youth with drug problems reported no treatment history related to substance abuse, and of the 26% that had received treatment, it just involved one treatment episode.

Cognitive-Behavioral Treatment for Dual Diagnosis Treatment

General Introduction to Dual Diagnosis Treatment. For a more effective clinical outcome and reliable prevention of relapse in adolescents and young adults using alcohol and drugs, a long-term treatment for SUD is usually necessary (Crits-Christoph et al., 1997; Crits-Christoph et al., 1999). Although effective agonist and antagonist pharmacotherapies as well as symptomatic treatments exist for opioid dependence (e.g., methadone or suboxone maintenance in heroin and/or prescription opiate addiction), neither agonists nor antagonists have been approved as uniquely effective for the treatment of stimulant dependence (Grabowski, Shearer, Merrill, & Negus, 2004). Because no proven effective pharmacological interventions are available for cocaine or methamphetamine addiction, treatment of stimulant addiction has to rely on existing cognitive-behavioral therapies (CBT), or CBT combined with other behavioral approaches (Van den Brink & van Ree, 2003). Other psychotherapeutic and psychosocial treatments may also be useful. The best current intervention

for cannabis abuse is oriented also at behavioral approaches rather than pharmacotherapy.

Treatment of a comorbid mental condition may also require the concurrent treatment of drug addiction (Trudeau, 2005a). In some cases, however, comorbid drug addiction may result from attempts to alleviate the psychiatric disorder through self-medication (i.e., co-occurring amphetamine use and ADHD; Khantzian, 1985, 1997). In many other cases, however, the severity of the comorbid psychiatric symptoms may increase as a consequence of drug abuse (Volkow, Fowler, & Wang, 2003, 2004). In dual-diagnosed patients with drug abuse arising from an attempt to self-medicate, treatment of the comorbid mental disorder may prevent abuse. For instance, treatment of the preexisting condition of ADHD in childhood and adolescence may prevent psychostimulant abuse in adulthood (Biederman et al., 1995; Biederman et al., 1997; Trudeau, Thuras, & Stockley, 1999). The co-occurrence of ADHD and SUD has received considerable attention in recent clinical and scientific literature (Davids et al., 2005). These two disorders are often linked to one another, and because the core symptoms of ADHD may be mimicked by the effects of psychoactive drugs, it is difficult to diagnose one disorder in the presence of the other (Davids et al., 2005). ADHD has been found to be associated with an earlier onset of SUD (Horner & Scheibe, 1997; Mannuzza, Klein, Bessler, Malloy, & LaPadula, 1998; Trudeau, 2005a, 2005b).

Dual Diagnosis Treatment Specifics in Adolescents. As was previously stated, ADHD is highly prevalent in populations with SUD and is associated with more severe course of the syndrome (Mariani & Levin, 2007). Persons with a co-occurring psychiatric disorder and SUD in general have a more persistent illness course, because the associated social and behavioral problems can make them more refractive to treatment than those without dual diagnosis (Brown, Recupero, & Stout, 1995; Everitt et al., 2008; O'Brien et al., 2004; Schubiner et al., 2000; Stevens, Schwebel, & Ruiz, 2007; Swartz & Lurigio, 1999; Wilens, Adler, Adams et al., 2008; Wilens, Adler,

Weiss et al., 2008). Clinicians must be more cognizant of the complicated nature of diagnosis and treatment of ADHD when it is comorbid with SUD. Pharmacotherapy, primarily in the form of psychostimulants such as methylphenidate, remains the mainstream treatment for ADHD (Levin, Evans, Brooks, & Garawi, 2007; Mariani & Levin, 2007; P. D. Riggs & Jellinek, 1998), though there have been also developments in complementary psychotherapeutic and applied psychophysiological (e.g., neurofeedback) approaches (Arns, de Ridder, Strehi, Breteler, & Coenen, 2009; Sherlin et al., 2010; Van den Bergh, 2010). There have been several case reports and open label clinical trials of methylphenidate for the treatment of patients with SUD and comorbid ADHD, suggesting that treatment with methylphenidate may lead to a reduction in drug use as well as in the ADHD symptoms (Castaneda, Levy, Hardy, & Trujillo, 2000; Levin & Kleber, 1995; Levin, Evans, Mcdowell, & Kleber, 1998; Schubiner et al., 2000; Schwebel, 2004; Somoza et al., 2004). However, many clinicians are very reluctant to prescribe stimulants to adolescent patients with drug abuse record, especially to those with history of prescription medication misuse and diversions (Kollins, 2008; Wilens, Adler, Weiss et al., 2008).

Alternative Adjunct Biobehavioral Treatment Approaches. Neurofeedback training-based neurotherapy is one of the potentially efficacious nonpharmacological treatment options for SUD (E. Sokhadze, Stewart, & Hollifield, 2007; T. M. Sokhadze, Cannon, & Trudeau, 2008; Trudeau, Sokhadze, & Cannon, 2008). There have been an increasing number of neurofeedback protocols that report success in treating a variety of addictive behaviors. A detailed review and historical perspectives on neurofeedback application for addictive disorders in adolescents can be found in Trudeau (2005a). Neurofeedback is promising as a treatment modality for adolescents, especially those with stimulant abuse and attention and conduct problems (Trudeau, 2005a). There is practically no literature on the use of neurofeedback in adolescent addictions, and the only information available comes from studies published on adult

addiction treatment. Neurofeedback has been studied as a method for treatment of addictive disorders in adults over the past 20 years or so, with a slowly accumulating body of evidence supporting its use in different circumstances. Several recent reviews (E. Sokhadze et al., 2007; T. M. Sokhadze et al., 2008; Trudeau, 2000a, 2000b, 2005a, 2005b; Trudeau et al., 2008) have detailed the literature regarding its use and the development of neurofeedback for addictive disorders.

Neurofeedback techniques for SUD may be of special interest for adolescent medicine because of the high comorbidity of SUD and ADHD in adolescents (Trudeau, 2005a). Considerable scientific effort has been directed at developing effective treatments for ADHD (Heinrich, Gevensleben, & Strehl, 2007; Holtmann & Stadler, 2006; Leins et al., 2007). Among alternative treatment approaches, neurofeedback has gained promising empirical support in recent years (Arns et al., 2009; Fox, Tharp, & Fox, 2005; Lubar, 2004; Monastra, 2003; Monastra, Lubar, & Linden, 2001; van den Bergh, 2010; J. M. Williams, 2010). Short-term effects were shown to be comparable to those of stimulant medication at the behavioral and neuropsychological level, leading to significant decreases of inattention, hyperactivity, and impulsivity (Fuchs, Birbaumer, Lutzenberger, Gruzelier, & Kaiser, 2003; Gevensleben, Holl, Albrecht, Schlamp et al., 2009; Gevensleben et al., 2010; Gevensleben, Holl, Albrecht, Vogel et al., 2009; Linden, Habib, & Radojevic, 1996; Monastra et al., 2002).

In addition, neurofeedback results in concomitant improvement of neurophysiological patterns. Kropotov et al. (2005) studied 86 children with ADHD after 15 to 22 sessions of EEG biofeedback (15–18 Hz) in an ERP Go/No-Go task. The ERP differences between post- and pretreatment conditions for good performers were distributed over frontal-central areas and appear to reflect the activation of frontal cortical areas associated with beta training. A controlled study was published using functional MRI to document positive changes in brain function in addition to behavioral changes in ADHD children following neurofeedback—changes

that were not found in a control group (Levesque, Beauregard, & Mensour, 2006). Several studies (Fuchs et al., 2003; Monastra et al., 2001; Monastra et al., 2005) demonstrated that neurofeedback produced improvements compared to Ritalin. EEG biofeedback may already be used within a multimodal setting, providing affected children and adolescents with a means of learning to counterbalance their ADHD symptoms without side effects. There is still a strong need for more empirically and methodologically sound evaluation studies. The techniques that combine classic ADHD neurofeedback approaches with addiction neurofeedback approaches hold special interest for SUD adolescents. They are medication free and thus minimize opportunities for medication abuse, both by inappropriate self-overdose and by trading medication for other substances. Neurofeedback techniques may have special applicability in attempting to treat the constellation of conduct disorder, nonalcohol SUD, and ADHD in already stimulant abusing teens. Trudeau (2000b) reported on the high incidence of childhood ADHD in a sample of chronic SUD adults and found that childhood ADHD status in this population predicted adult stimulant abuse. This research sample supports other literature finding a significant overrepresentation of adults and adolescents with comorbid ADHD and SUD and also children with ADHD who eventually develop SUD (Barkley, Fischer, Edelbrock, & Smallish, 1990; Biederman, 2003; Biederman et al., 1995; Carroll & Rounsaville, 1993; Mannuzza et al., 1998). By providing low-risk and medication-free therapy for both ADHD and SUD, neurofeedback becomes another treatment option open to practitioners reluctant to prescribe controlled substances to ADHD adolescents at risk for or with SUD.

ELECTROENCEPHALOGRAPHIC AND ERP STUDIES IN ADHD, CD, SUD, AND DUAL DIAGNOSIS

EEG and ERP in ADHD and CD

EEG.   EEG power studies have found fairly consistent group differences between children

with and without ADHD (Barry, Clarke, & Johnstone, 2003a, 2003b; Barry et al., 2007). The major differences include increased theta activity primarily in the frontal regions, increased posterior delta, and decreased alpha and beta activity in the posterior regions (Barry et al., 2007; Chabot & Serfontein, 1996; Clarke, Barry, McCarthy, & Selikowitz, 1998, 2001, 2002; Clarke, Barry, McCarthy, Selikowitz, & Brown, 2002; Lazzaro et al., 1998; Mann, Lubar, Zimmerman, Miller, & Muenchen, 1992). Ratios between frequency bands have also been used to assess differences in the EEG of normal children and children with ADHD. An increase in both the theta/alpha and theta/beta ratios has been found in ADHD (Barry et al., 2007; Lubar, 2003, 2004). Although such EEG studies have found consistent differences between children with and without ADHD, attention deficit is often a highly comorbid disorder, being found in conjunction with anxiety and depressive disorders, learning disabilities (Biederman et al., 1995), and CD or ODD (Jensen et al., 1997).

Models of brain function in ADHD emphasize frontal/parietal interactions in deficits of attention (Shaw et al., 2006; Silberstein et al., 1998) and anterior cingulate/lateral prefrontal cortex interactions in behavioral disinhibition (Barkley, 1997; L. M. Williams, 2006). Mechanisms of large-scale coordination between cortical areas can be explored via measures of specific frequency waves in the EEG. Previous EEG, ERP, and fMRI research has contributed to the understanding of impairments in attention, executive functions, and memory in children and adolescents with ADHD (Konrad, Neufang, Hanisch, Fink, & Herpertz-Dahlmann, 2006; Lenz et al., 2008). However, there is a lack of studies investigating ADHD-related differences in the gamma range of EEG, although gamma oscillations are directly associated with cognitive processes impaired in ADHD patients (Keizer, Verment, & Hommel, 2010). Lenz et al. (2008) studied the encoding phase of a visual memory paradigm in ADHD patients and found a strong task-related enhancement of evoked gamma for ADHD patients. This could indicate a decrease in the neuronal signal-to-noise ratio partially

caused by the genetic variations within the dopaminergic pathway of ADHD patients. Genetic polymorphisms have been shown to modulate evoked gamma responses, which therefore could be a possible marker of impaired neurotransmission in ADHD. Deviations of gamma responses indicate that early mechanisms of sensory stimulus processing are altered in ADHD as a result of impaired motor inhibition (Yordanova, Banaschewski, Kolev, Woerner, & Rothenberger, 2001).

Few studies have compared EEG differences in ADHD children with or without comorbid CD or ODD. Satterfield, Schell, and Nicholas (1984) investigated EEG of hyperactive adolescents, both with and without signs of disruptive behavior. The nondelinquent hyperactive group had higher total power and absolute alpha and beta, higher relative alpha and beta, and less relative theta compared with normal control subjects. The EEG of the CD hyperactive group were similar to those of the control group. From these results it was concluded that hyperactive children with abnormal EEG have a childhood disorder that is secondary to an underlying brain dysfunction typical for ADHD. In comparison to this, the group with disruptive behaviors without ADHD and with normal EEG has a childhood disorder secondary to an underlying environmental–social factor.

Children with ADHD have been found to have increased slow wave and decreased fast wave activity in EEG when compared with normal children (Clarke, Barry, McCarthy, & Selikowitz, 2002; Clarke, Barry, McCarthy, Selikowitz, & Brown, 2002). The theta/alpha and theta/beta ratios have also been used as markers of maturational changes in the EEG and as an identifier of ADHD (Clarke et al., 2001; Lubar, 2003). Most studies of children with a diagnosis of CD or ODD have failed to find any EEG differences between their clinical groups and normal children (Hsu, Wisner, Richey, & Goldstein, 1985; Satterfield et al., 1984; Satterfield, Schell, Nicholas, Satterfield, & Freese, 1990). From these EEG studies, CD or ODD was not viewed as having an electrophysiological component, which suggested

that the disorders resulted from a social–environmental factor rather than abnormal neural functioning expressed in an altered EEG (Satterfield et al., 1984). In the studies of Clarke, Barry, McCarthy, and Selikowitz (2002) and Clarke, Barry, McCarthy, Selikowitz, and Brown (2002), the ADHD-ODD comorbidity group had differences in their EEG when compared with normal children. However, these differences appeared to reflect the ADHD component of the diagnosis rather than the ODD component. Only two significant topographic EEG differences were found between the ADHD groups, with both of these being less deviant from normality in the ADHD-ODD group than the ADHD group. These results indicate that EEG correlates of ADHD are not clouded according to Clarke, Barry, McCarthy, and Selikowitz (2002) by the presence of comorbid ODD, which suggests possible applications in clinical practice for diagnostic and outcome measurement.

ERP. Children with ADHD have been shown to differ from controls on most components during attention-based tasks. Brain research studies using ERPs reported that despite some ERP differences, a dysfunctional attention system is not the major cause of ADHD (Nigg, 2005). ERP studies have indicated inhibition problems in children with ADHD, including an altered frontal P300 (Okazaki, Ozaki, Maekawa, & Futakami, 2004). These results support the theory that behavioral inhibition might be deficient in ADHD, as children with ADHD show abnormalities in inhibitory ERPs related to the effort involved in inhibiting a motor response in Go/No-Go or Stop-signal type tasks. Compared to healthy controls, latencies of P200, N200, and P300 were prolonged in auditory oddball tasks, whereas the amplitude of P300 was reduced in the comorbid ADHD-CD group (Du et al., 2006). These findings are in accordance with reports about the abnormalities of the classical parietal P3b in adolescents with ADHD (Brandeis et al., 2002; Strandburg et al., 1996) but are discordant with the other findings in those with ADHD-CD comorbidity (Banaschewski et al., 2003; Rothenberger

et al., 2000). Of interest, teenagers with CD diagnosis did not differ significantly from teenagers without CD in the magnitude of either Stroop test inhibition or facilitation ERP markers. One interpretation of this pattern of results suggests that the cognitive deficit associated with CD might not be specifically tied to response inhibition/facilitation, but rather the deficit may involve a more generalized disturbance of attention or resource allocation (Bauer & Hesselbrock, 1999; Burgess et al., 2010).

The response-locked error-related negativity is a negative-going waveform peaking 40 to 140 ms after an error response or negative feedback stimulus (Falkenstein, Hoormann, Christ, & Hohnsbein, 2000; Falkenstein, Hoormann, & Hohnsbein, 1999; Gehring & Knight, 2000). This component is thought to reflect a mismatch between actual and intended actions or goals and, therefore, occurs in response to unfavorable outcomes, response errors, response conflict, and decision uncertainty (Ridderinkhof, Ullsperger, Crone, & Nieuwenhuis, 2004). The error-related negativity is hypothesized to reflect phasic anterior cingulate cortex activity in response to reinforcement signals from the mesencephalic dopamine system that serves as a trigger for further processing of the event and further deliberate compensatory behavior (Holroyd & Coles, 2002). Two studies have found reduced error-related negativity amplitudes in children with ADHD compared to typical children, suggesting that they have a deficit in monitoring ongoing behavior (Liotti, Pliszka, Higgins, Perez, & Semrud-Clikeman, 2010; Van Meel, Heslenfeld, Oosteriaan, & Sergeant, 2007). Reduced error awareness may thus compromise children with ADHD in adequately adapting their behavior and consequently in learning from their mistakes.

EEG and ERP in SUD

EEG. The current review by Başar and Güntekin (2008) includes analysis of EEG oscillations in ADHD, alcoholism, substance abuse, and other psychiatric disorders. Several studies of substance abuse have used qEEG in adolescent and young adult substance abusers. Ehlers and Criado (2010) recently reviewed

electrophysiological effects produced by adolescent alcohol exposure. The animal model studies reviewed provide evidence that demonstrates that relatively brief exposure to high levels of ethanol during a period corresponding to parts of adolescence in the rat is sufficient to cause long-lasting changes in functional brain activity. Replicated human studies reports have appeared of increased beta relative power in alcohol dependence (Bauer & Hesselbrock, 1993; Chabot, di Michele, & Prichep, 2005; Coger, Dymond, & Serafetinides, 1978, 1979; Franken, Stam, Hendriks, & van den Brink, 2004; Gabrielli, Mednick, & Volavka, 1982). Increased alpha power, especially in frontal regions, has been reported in withdrawal and after acute exposure to marijuana (Struve, Straumanis, & Patric, 1994; Struve, Straumanis, Patric, & Price, 1989). Increased alpha and decreased delta and theta have been reported in crack cocaine users during acute withdrawal (Alper, Chabot, Kim, Prichep, & John, 1990, 1993; Cornwell, Roemer, Jackson, & Dewart, 1994; Prichep et al., 1996; Roemer, Cornwell, Jackson, & Dewart, 1994). Quantitative EEG shows several marked abnormalities in alcohol and substance abuse. The effects are largely dependent on the class of drugs used. Either increased slow activity with lower alpha and beta or the converse has been reported, which reflects diversity of substances studied and the differences in topography of EEG or substance use severity states. There is an agreement among researchers regarding increased beta relative power in alcoholism and increased alpha in chronic cannabis or crack cocaine users. In studies of Prichep et al. (2002), a chronic crack cocaine–dependent population was divided by age of first use. The qEEGs contained significantly more theta excess in individuals who started using as adolescents, which suggests enhanced vulnerability for such effects on brain function (Prichep et al., 1996; Prichep et al., 2002). A significantly larger proportion of the group that began using drugs as adolescents was found to have a history or current signs of ADHD (Chabot et al., 2005). Clear differences were reported between crack cocaine–dependent subjects who began using

as adolescents and subjects who began using as adults. EEG effects of chronic marijuana users during abstinence are reported to be associated with reduced power in alpha and beta bands at posterior sites (Herning, Better, & Cadet, 2008). Chronic marijuana users were earlier found to have an increase in frontal EEG alpha power (Struve et al., 1994). More detailed description of acute and chronic neurotoxic effects of specific psychostimulant substances on qEEG in adults can be found in our previous reviews (E. Sokhadze et al., 2007; T. M. Sokhadze et al., 2008; Trudeau, 2000b, 2005b).

ERP. ERP studies have found a reduced amplitude of the P300 waveform among adult alcoholics compared with nonalcoholic control subjects (Begleiter & Porjesz, 1995). Similar reductions in P300 ERP amplitude have been reported among the unaffected biological offspring of an alcoholic parent (Begleiter, Porjesz, Bihari, & Kissin, 1984; Carlson, Iacono, & McGue, 2002; Hill, Yuan, & Locke, 1999; O'Connor, Bauer, Tasman, & Hesselbrock, 1994) and in relation to a personal diagnosis of antisocial personality disorder (Bauer, O'Connor, & Hesselbrock, 1994). Response inhibition is considered a core dimension in alcoholism and its coexisting disorders. Using a visual Go/No-Go task, Rangaswamy, Stimus, and Begleiter (2005) showed that alcoholics manifest a decreased P300 amplitude during Go as well as No-Go conditions (No-Go P3; Falkenstein et al., 1999). The difference between Go and No-Go processing was more evident in controls than in alcoholics. The topography of current source density in alcoholics during the No-Go P3 response was found to be very different from that of controls, suggesting that alcoholics perhaps activated inappropriate brain circuitry during cognitive processing. The reduced No-Go P3 along with the relatively less anteriorized topography during No-Go condition suggests poor inhibitory control, and it is proposed that the No-Go P3, the electrocortical signature of response inhibition, can be considered as an endophenotypic marker in alcoholism in those genetically predisposed to SUD (Kamarajan et al., 2004; Kamarajan et al., 2006; Rangaswamy et al., 2005).

Many studies have shown that youths who are at high risk for SUD have attenuated P300 amplitude ascertained on the basis of parental history of SUD (Begleiter et al., 1984; Hada, Porjesz, Begleiter, & Polich, 2000; Hill et al., 1999). The hypothesis has been advanced that low P300 amplitude observed in high-risk individuals reflects disrupted inhibitory mechanisms (Begleiter & Porjesz, 1995). However, psychopathological disorders having the salient characteristic of impaired inhibitory regulation, such as CD and antisocial personality disorder (Bauer, 1997; Bauer & Hesselbrock, 2001, 2002; Bauer et al., 1994; Iacono, Carlson, Malone, & McGue, 2002; Kim, Kim, & Kwon, 2001), are also featured by diminished P300. In effect, the extent to which P300 amplitude predicts SUD directly or is one facet of a general disinhibitory disposition concomitant to SUD risk remains to be determined. Moreover, a significant correlation has been observed between P300 and disinhibition severity (Habeych, Charles, Sclabassi, Kirisci, & Tarter, 2005). Nevertheless, it is presently not known whether behavioral disinhibition entirely accounts for the association between P300 in childhood and adolescence and SUD outcome or instead whether there is also a specific direct association.

RATIONALE OF APPLICABILITY OF NEUROFEEDBACK FOR SUBSTANCE ABUSING ADOLESCENTS WITH BEHAVIORAL PROBLEMS

Approach to Treatment of Substance Abusing Adolescents with Disruptive Behaviors

Based on our prior pilot research on neurofeedback therapy in addiction (Finkelberg et al., 1996; E. M. Sokhadze, 2005; E. Sokhadze et al., 2007; T. M. Sokhadze et al., 2008; Trudeau et al., 2008) and more recent studies on behavioral interventions based on the effects of motivational interviewing (Miller & Rollnick, 2002) in cocaine-dependent subjects (E. M. Sokhadze, 2005; E. Sokhadze, Stewart, Hollifield, & Tasman, 2008; E. Sokhadze, Stewart, Sokhadze, Husk, & Tasman, 2009;

E. Sokhadze et al., 2010; Horrell, Sokhadze, Stewart, El-Baz, & Tasman, 2010) and in ADHD (G. Sokhadze et al., 2010), we propose that the combined application of neurofeedback with an appropriate CBT technique will result in an effective biobehavioral intervention for adolescent addicts with ADHD and/or CD comorbidity. There are currently several CBT programs that can be used in a community mental health services for adolescents (Becker & Curry, 2008), such as, for example, Seven Challenges® (Schwebel, 2004). The Seven Challenges is a cognitive-behavioral treatment for adolescents with co-occurring substance abuse and mental health problems developed by Dr. Schwebel (Prochaska, DiClemete, & Norcross, 1992; Schwebel, 2004; Stevens & Ruiz, 2006). The Seven Challenges is a nationally recognized program, listed on SAMHSA's National Registry of Evidence Based Practices. The program has been shown to be especially effective for youth with co-occurring disorders.

Adolescent patients with a co-occurring mental condition and drug addiction are more resistant to treatment and are reluctant to enter either inpatient or outpatient treatment programs than those without dual diagnosis (Brown et al., 1995; O'Brien et al., 2004; Schubiner et al., 2000; Swartz & Lurigio, 1999). CBT may enhance remediation of behavioral problems that complicate engagement of dually diagnosed adolescents in treatment. ADHD alone significantly increases the risk for SUD (Biederman et al., 1995). Associated social and behavioral problems may make individuals with comorbid SUD and ADHD treatment resistant (Wilens, Biederman, & Mick, 1998). In male individuals ages 16 to 23, the presence of childhood ADHD and CD is associated with nonalcohol SUD (Gittelman et al., 1985; Mannuzza et al., 1989). The incidence of ADHD in clinical SUD populations has been studied and may be as high as 50% for adults (Downey, Stelson, Pomerleau, & Giordani, 1997) and adolescents (Horner & Scheibe, 1997). Adult residual ADHD is especially associated with cocaine abuse and other stimulant drug abuse (Levin & Kleber, 1995). Kalechstein et al. (2000) found that methamphetamine-dependent

individuals are at a greater risk of experiencing particular psychiatric symptoms. There are no published systematic studies of neurofeedback treatment of co-occurring depression, ADHD, posttraumatic stress disorder, or CD on the course and outcome of addiction.

Therefore, treatment of adolescent patients with SUD using neurofeedback may become more complicated when patients present various psychiatric conditions. When addiction is comorbid with ADHD it is suggested that sensorimotor rhythm or beta increase and theta decrease training should be conducted to address the ADHD symptoms first (Trudeau, 2005a). More research needs to be done to determine the clinical outcome and efficacy of biobehavioral treatment based on brain wave self-regulation in SUD comorbid with disruptive behavioral disorders; this needs to be done first in SUD co-occurring with ADHD, as ADHD is very often accompanied with comorbid CD and ODD conditions.

Although there is little work available on the prevention and treatment of SUD in adolescents and children utilizing neurofeedback, there is no reason to suspect that the applicability of the approaches used in adults would not be applicable in SUD adolescents (Trudeau, 2005a). There has been only one unpublished report of brain wave biofeedback used to treat co-occurring ADHD and conduct problems in adolescents with SUD (Martin, 2003). The study did not address the issue of SUD per se, and outcome data regarding long-term follow-up of substance use status are not available. One study of behavioral control in adult offenders using EEG biofeedback techniques is published (Quirk, 1995), again suggesting the utility of the approach of neurofeedback in settings where conduct/behavior problems are of concern.

Adolescent alcohol abusers who do not have features of ADHD or nonalcohol drug abusers may be as responsive to neurofeedback protocols as adult alcoholics. Several studies demonstrated effects of neurofeedback in adult drug abusers (Bodenhamer-Davis & Callaway, 2004; Burkett, Cummins, Dickson, & Skolnik, 2005; Horrell et al., 2010; Peniston & Kulkosky,

1989, 1991; Scott, Kaiser, Othmer, & Sideroff, 2005; E. Sokhadze et al., 2009). Untreated ADHD, especially with hyperactivity and CD in male individuals, is a risk factor for SUD (Mannuzza et al., 1998; Mannuzza et al., 1991). Neurofeedback treatment of ADHD may be important in prevention for children and adolescents at risk for developing SUD. Stimulant medication treatment of ADHD in children has been shown to not increase subsequent SUD (Mannuzza et al., 2003). In fact, stimulant therapy protected medicated ADHD patients against SUD, which occurred at rates that were 3 to 4 times greater among people with untreated ADHD (Biederman, 2003). It may be possible that neurofeedback of childhood ADHD is also associated with a decrease in later life SUD.

Neurofeedback of ADHD in children and adolescents has recently been reviewed extensively (Arns et al., 2009; Lubar, 2003; Monastra, 2003; Sherlin, Arns, Lubar, & Sokhadze, 2010; J. M. Williams, 2010). To date, several controlled-group studies (Fuchs et al., 2003; Gevensleben, Holl, Albrecht, Schlamp et al., 2009; Gevensleben et al., 2010; Gevensleben, Holl, Albrecht, Vogel et al., 2009; Linden et al., 1996; Monastra et al., 2002; Rossiter & LaVaque, 1995) have been reported in peer-reviewed journals. Each of these studies sought to examine the effects of neurofeedback in the treatment of patients with ADHD while attempting to control for certain factors (e.g., age, intelligence, severity of symptoms prior to initiating treatment). Maturation effects were also controlled in each of these studies and comparisons with stimulant medication were included in three of the four studies. There have been no reported studies of the effect of neurofeedback treatment on prevention of SUD to date.

EEG biofeedback of ADHD may be medication free or combined with medication adjunctively. Neurofeedback may be a preferred approach for child and adolescent ADHD if stimulant medication abuse is suspected, or if side effects of medication are not tolerated, or if medication is not fully effective. It may also be the choice of

patients and therapists who prefer nonmedication treatments. Side effects commonly associated with medication (such as growth retardation, poor appetite, sleep disturbances, etc.) have not been reported with neurofeedback.

Research Needed to Delineate Mechanisms of Change in Adolescents Undergoing Integrated Biobehavioral Therapy

Research studies using randomized clinical trials allow for evaluating the efficacy of behavioral treatments in substance abuse, behavioral disorders, and their comorbidities. They also can be valuable in revealing moderators and mediators of therapeutic change (Kraemer, Wilson, Fairburn, & Agras, 2002; Ridenour, Hall, & Bost, 2009). However, little is known about patient characteristics (including comorbidity) that predict or moderate treatment effects. Although operant conditioning theory posits that changes in EEG patterns can be learned using instrumental conditioning paradigm (Hoedlmoser et al., 2008), it is not sufficiently well explored how changes in specific EEG frequencies mediate the effects of neurofeedback on patient outcomes in ADHD and substance abuse. Pre- to posttreatment changes in sensorimotor rhythm (12–15 Hz), theta (4–7 Hz), and high frequency EEG (beta, 13–30 Hz, gamma, 30–45 Hz) are considered to positively affect motor control, cortical inhibition function, general arousal, and alertness level. This mediates the positive effects of proposed neurofeedback protocol on ADHD symptoms and addictive behaviors.

The mechanisms of therapeutic change are rarely studied in adolescent therapy (Kazdin & Nock, 2003), and application of cognitive neuroscience methods is an important objective for improving clinical practice and adolescent patient care. Extension of clinical treatment trials to any clinical or community treatment settings, without complementary research that studies why and how treatment works, could have great limitations. The logistic of any sound methodology should address questions of identifying possible mechanisms and provide information for why or how treatment works using behavioral, clinical, neurocognitive, and EEG/ERP data. In psychotherapy research, and applied neuroscience research more generally, mediator is often used as a construct intended to signify a cause or mechanism of change and distinguished from moderator. By mechanisms of action, we refer to those behavioral, cognitive, or psychophysiological processes that lead to and cause expected therapeutic change in our population under study. Normative heterogeneity and specifics in the time-course of neurodevelopmental processes appears to be one of major contributors to adolescent substance abuse vulnerability (N. R. Riggs & Greenberg, 2009; P. D. Riggs & Jellinek, 1998) because frontal cortical areas related to processing reward, pleasure, novelty seeking, and emotion achieve functional maturity much earlier in development than do frontal areas responsible for self-regulation of behavior and higher order cognitive decision making. Future studies should consider normative developmental executive cognitive function delays as a moderator of adolescent substance use and ADHD treatment outcomes and offer a way to find mediating mechanisms through behavioral and neurofeedback-based training of executive self-control.

Furthermore, there have been several quantitative electroencephalographic and ERP-based biological markers identified that indicate the risk of developing alcohol and drug abuse, and they are often linked to a history of childhood behavioral problems (including ADHD). These qEEG and ERP biomarkers are of specific interest to neurotherapy specialists. According to Lenz and colleagues (Lenz et al., 2010; Lenz et al., 2008), even in the era of fMRI, the EEG still represents an important tool for brain research for neurology and psychiatry. Some diseases can be more easily identified with EEG than with functional imaging, especially when the disease manifests in a form of altered electrical brain activity such as in ADHD. The new trends in cognitive neuroscience make it possible to study neural network dynamics in the human brain in mental disorders, and specifically in ADHD,

disruptive behaviors, and substance use disorders (Banaschewski & Brandeis, 2007; Herrmann & Demiralp, 2005; Keizer et al., 2010; Prichep & John, 1997).

Strategies of Neurofeedback-Based Intervention

Strengthening Executive Functions. We propose utility of such clinical research directions for the development and implementation of substance use and ADHD treatment approaches in adolescence that specifically target development and strengthening of executive functions using operant conditioning of specific EEG frequencies and cognitive-behavioral remediation of social functioning domain using CBT. Furthermore, pretreatment, posttreatment, and follow-up assessments using clinical, behavioral, and specific executive and emotional functioning tests should be used to provide insight on possible mediators and moderators of the integrated intervention outcome. We propose that behavioral, cognitive, and emotional functions should be considered among the possible mediators of effects on substance abuse outcomes because our proposed integrated treatment promotes neurocognitive efficiency, first of all, by providing adolescents with the opportunity to practice skills related to frontal lobe development and executive function through EEG training and behavioral skills training, which in turn is significantly related to a decrease in substance abuse and aberrant behaviors. Few, if any, substance abuse interventions explicitly intend to promote the development of cognitive abilities using intensive and specific training based on real-time EEG analysis. We advocate an integrated intervention to promote skills such as conscious strategies for self-control, attention, concentration, and problem solving, which may ultimately aid in the development of adolescents' neurocognitive capabilities.

Understanding Role of Self-Regulation Deficits in ADHD and SUD. Current theoretical models of ADHD suggest that a core deficit is not attention as such, but rather disruption of executive functions, and in particular behavioral

inhibition deficit. Converging evidence supports the view that ADHD is related to atypical development of cognitive control along fronto-striatal networks. The resulting deficit is presented by a combination of hypofunctional "top-down" executive processes (e.g., inhibition) regulated by the frontal lobe, and hypofunctional "bottom-up" regulation (e.g., activation) regulated by the brainstem and thalamo-cortical pathways (Barkley, 1997). New theoretical concepts in ADHD outline that "*this syndrome is not seen as a disorder of attention at all, but as a disorder in key aspects of self-regulation*" (Nigg, 2005, p. 1424). The same self-regulation deficits occur in SUD, and of course in conduct disorder. Although qEEG studies present well-documented differences between ADHD and control adolescents, it is very likely that more profound differences of EEG markers will be manifested during performance of specific tests, for example, executive function tests where electrocortical abnormalities of both ADHD and SUD patients are visible and expressed better. In addition to attentional and cognitive impairment, there are disruptions in processing emotion and mood abnormalities in individuals with ADHD (L. M. Williams et al., 2008), CD, ODD, and substance abuse, but still little is known about the neural basis of these affective impairments.

Previous EEG and ERP research has contributed to the understanding of impairments in attention, executive functions, and memory in ADHD (Lenz et al., 2008). It is necessary to bring together clinical, behavioral, qEEG, ERP, and neurocognitive measures to examine the effects of integrated biobehavioral treatment in adolescents at high risk for substance dependence. Method of self-regulation of executive functions in vulnerable adolescents should be based on specific protocol that sets training goals resulting in improvement in attention, vigilance, lower hyperactivity, and skills to inhibit impulsive behavioral responses. The neurobiological nature of vulnerabilities for addiction (Goldstein & Volkow, 2002; Volkow & Fowler, 2000; Volkow et al., 2003, 2004), the high rate of comorbid ADHD, and the

negative impact of drugs on brain and behavior of youth make it extremely important to apply efforts to develop theoretically and practically sound early intervention methods. Neurofeedback, qEEG evaluations, and neurocognitive tests should constitute an important part of the treatment and outcome assessment.

Summary on Applicability of Neurofeedback for Adolescents with Drug and Behavior Problems. Although there is little work available on the prevention and treatment of substance abuse in adolescents utilizing neurofeedback, there is no reason to suspect that the applicability of the approaches used in adults would not be applicable in drug abusing adolescents. There have only been several unpublished reports of biofeedback used to treat co-occurring ADHD and conduct problems in adolescent drug abusers. We suggest the utility of the approach of neuromodulation in settings where conduct/behavior problems are of concern, and several studies demonstrated effects of neurofeedback in adult drug abusers. Because untreated ADHD is a risk factor for SUD, neurofeedback treatment of ADHD may be important in prevention for adolescents at risk for developing SUD. Neurofeedback of ADHD in children and adolescents has been reviewed extensively, and a recent meta-analysis concluded that neurofeedback in ADHD was shown to be superior to a credible placebo control (Arns et al., 2009) and was demonstrated in independent research settings, thereby meeting efficacious and specific treatment definition. Future studies using biobehavioral therapy that combines CBT and neurofeedback in adolescent drug and alcohol abuse treatment settings where SUD and ADHD often co-occur should be conducted to assess the clinical effectiveness and outcomes of this promising integrated technique. Self-regulation of brain activity has more potential in adolescence due to a higher level of neuroplasticity of neural systems at this age as compared to adult population.

Adolescent nonalcohol drug abusers with ADHD features may be as responsive to neurofeedback protocols as adult addicts. Several studies demonstrated effects of neurofeedback in adult drug abusers (Peniston & Kulkosky, 1989; Scott et al., 2005; E. Sokhadze et al., 2008; E. Sokhadze et al., 2009; E. Sokhadze et al., 2010; T. M. Sokhadze et al., 2008). Untreated ADHD, especially with hyperactivity and CD in male individuals, is a risk factor for SUD (Mannuzza et al., 1998). Recent studies have shown that adults who have been diagnosed with ADHD during childhood are overrepresented in samples of delinquents, drug addicts, and patients with personality disorders. These findings once more underscore the importance of early diagnostic of ADHD and adequate treatment of ADHD.

Neurofeedback treatment of ADHD may be important in prevention for children and adolescents at risk for developing SUD. Stimulant medication treatment of ADHD in children has been shown to not increase subsequent SUD (Mannuzza et al., 1998). In fact, stimulant therapy protected medicated ADHD patients against SUD, which occurred at rates that were 3 to 4 times greater among people with untreated ADHD (Biederman, 2003). It may be possible that neurofeedback of childhood ADHD is also associated with a decrease in later life SUD (Trudeau, 2005a). There have been no reported studies of the effect of neurofeedback treatment on prevention of SUD to date. We stated in our review of biofeedback field that ''one of the most significant potential of biofeedback-based methodology is its use for prevention and individual prophylaxis'' (Sokhadze & Shtark, 1991, p. 259), and this statement is especially true for high-risk adolescents.

EEG biofeedback of ADHD may be medication free, or combined with medication and/or CBT adjunctively. Neurofeedback may be a preferred approach for child and adolescent ADHD if stimulant medication abuse is suspected, or if side effects of medication are not tolerated, or if medication is not fully effective. It may also be the choice of patients and therapists who prefer nonmedication treatments. Side effects commonly associated with medication (such as growth retardation) have not been reported with neurofeedback. The crucial point about

neurofeedback is that it directly acts on the brain oscillations, which are altered in SUD and ADHD. Neurofeedback-induced modifications must be treated as a manifestation of neural plasticity—a phenomenon that we consider to be a basic mechanism for behavioral modifications.

CONCLUSIONS

Application of neurofeedback and/or integrated neurotherapy combining neurofeedback with CBT or other insight and behavior-based therapies may have important applications. Because it has the potential to improve attention, emotion, and behavior self-regulation skills in adolescents at high risk for addiction development and to prevent progression to SUD, this technique may be clinically relevant. Interventions that incorporate behavioral and neurofeedback techniques are aimed to reeducate adolescents to control and self-regulate their emotional and motivational states, and to reestablish the normal biological, cognitive, behavioral, and hedonic homeostasis distorted by drug abuse and disruptive behaviors. Future studies have to address whether integrated training that uses neurofeedback might be successfully applied to dually diagnosed patients with both SUD and other mental disorders, and whether observed changes are stable in the long term. The crucial point about this kind of combined biologic and behavioral therapy is that it directly acts on the brain oscillations, which are altered in SUD and ADHD. Future studies should focus on the effects of neurofeedback integrated with CBT on more extended sets of cognitive tasks and address the possible clinical significance of this kind of integrated biobehavioral training as a treatment arm for dually diagnosed subjects. We propose that a neurofeedback-based treatment approach represents a behavioral intervention to activate and strengthen circuits involved in inhibitory control, including self-regulation training directed at the normalization of frontal and central cortical activity, and this may improve ability to exercise executive functions and increase successful abstinence from abused

drugs. Considering the important role of endophenotypic cognitive and emotional specificities of individual traits rendering some adolescents at higher risk in terms of a predisposition for drug abuse, the development of nonpharmacological interventions (e.g., CBT, neurofeedback) seems to be a feasible strategy for drug abuse prevention. Self-regulation of brain activity may have even more potential in adolescence due to a higher level of neuroplasticity of neural systems at this age as compared to adult population.

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