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Stimulant drug action in attention deficit hyperactivity disorder (ADHD): inference of neurophysiological mechanisms via quantitative modelling

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Abstract

Objective: To infer the neural mechanisms underlying tonic transitions in the electroencephalogram (EEG) in 11 adolescents diagnosed with attention deficit hyperactivity disorder (ADHD) before and after treatment with stimulant medication.

Methods: A biophysical model was used to analyse electroencephalographic (EEG) measures of tonic brain activity at multiple scalp sites before and after treatment with medication.

Results: It was observed that stimulants had the affect of significantly reducing the parameter controlling activation in the intrathalamic pathway involving the thalamic reticular nucleus (TRN) and the parameter controlling excitatory cortical activity. The effect of stimulant medication was also found to be preferentially localized within subcortical nuclei projecting towards frontal and central scalp sites.

Conclusions: It is suggested that the action of stimulant medication occurs via suppression of the locus coeruleus, which in turn reduces stimulation of the TRN, and improves cortical arousal. The effects localized to frontal and central sites are consistent with the occurrence of frontal delta–theta EEG abnormalities in ADHD, and existing theories of hypoarousal.

Significance: To our knowledge, this is the first study where a detailed biophysical model of the brain has been used to estimate changes in neurophysiological parameters underlying the effects of stimulant medication in ADHD.

Keywords: Norepinephrine; Acetylcholine; Locus coeruleus; Thalamus; EEG; Thalamic reticular nucleus; Arousal; Cortex

1. Introduction

The most common form of treatment for attention deficit hyperactivity disorder (ADHD) is the use of stimulant medications (Kube et al., 2002; Rowland et al., 2002; Wilens and Spencer, 2000), typically dextroamphetamine (Dexedrine) or methylphenidate (Ritalin) (Connor, 2002; Pliszka et al., 2000; Smucker and Hedayat, 2001). These medications are believed to improve ADHD symptoms by increasing arousal and alertness of the central nervous system through the stimulation of the noradrenergic (NA) and dopaminergic (DA) systems (Biederman and Spencer, 1999; Pliszka et al., 1996). Scalp recordings of the electroencephalogram (EEG), as an index of neural activity, have been a useful measure for assessing the effects of stimulant medications (Chabot et al., 1999; Clarke et al., 2002b; Satterfield et al., 1973). These studies have shown that those individuals who best respond to treatment have an abnormally high level of delta–theta EEG power, and low skin conductance level, suggesting a condition of cortical hypoarousal. Other studies have indicated that stimulant medications can act to normalize the theta and beta EEG abnormalities in children with ADHD (Clarke et al., 2002a, 2003; Loo et al., 1999; Lubar et al., 1999). However, the above studies have been unable to determine explicit mechanisms underlying such abnormalities or the neurophysiological effects of stimulant medications.

In a previous study it was argued that cortical hypoarousal in ADHD occurs due to increased activity of

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cortical networks involving inhibitory neurons, including those in the thalamic reticular nucleus (TRN) (Rowe et al., 2004a,c). Other researchers (McCormick, 1989; Sherman and Guillery, 2001; Steriade et al., 1991) and recent work using the same biophysical model of the cortex (Robinson et al., 2001b, 2004; Rowe et al., 2004b) have shown that increased inhibitory activity from the TRN in particular, is directly involved in the generation of delta–theta activity during reduced states of arousal. These findings motivated a previous study exploring the occurrence similar neural mechanisms underlying cortical dysfunction and the delta–theta EEG abnormalities in ADHD subjects (Rowe et al., 2004a,c). In this work, the same biophysical model was used to fit and replicate the EEGs from 54 adolescent unmedicated ADHD subjects and age- and sex-matched healthy controls. In the ADHD group, the results confirmed an abnormal increase in the activity of short range inhibitory and excitatory stellate cells and neurons in the TRN (Rowe et al., 2004a). These results were also associated with findings showing a significant slowing of dendritic responses, consistent with the smaller synapto-dendritic rate constants of inhibitory GABA type neurons (particularly $GABA_B$) compared with excitatory AMPA (Thomson, 1997; Thomson et al., 1996). In another prior study, activity in the intrathalamic network involving the TRN was also found to be positively correlated with increases in delta–theta EEG power (Rowe et al., 2004b), consistent with the delta–theta abnormalities in ADHD. In conclusion, over-activity in the intrathalamic network was suggested to occur due to a tonic over-stimulation of the TRN by the locus coeruleus (LC) NA projections. This proposal is consistent with studies showing LC neurons can increase TRN activity (Destexhe et al., 1994; McCormick, 1989; Sherman and Guillery, 2001), and other work suggesting a LC *overdrive* in ADHD, and the proposed antagonistic effects of stimulant medication upon LC activity (Konrad et al., 2003; Pliszka et al., 1996; Solanto, 1998).

In Rowe et al. (2004a,c) the possible neural mechanisms underlying the signal processing deficits found in ADHD was also examined (Pliszka et al., 1996; Volkow et al., 2001). The results from the modelling EEGs in the ADHD subjects indicated an overactivity in cortical networks, particularly relating to local inhibitory and excitatory interneurons or stellate cells (Rowe et al., 2004a). It was concluded that an overactivity of cortical neurons may occur due to a deficit in the activation of NA and cholinergic metabotropic receptor activity, and this may interfere with signal processing. Activation of these receptors normally suppresses the firing activity of their target neurons by reducing neurotransmitter release (Curet et al., 1992; Hasselmo and Fehlau, 2001; Koós and Tepper, 2002; Murakoshi, 1995). Therefore, these studies suggest that stimulant medications can assist signal processing functions in ADHD by increasing extracellular norepinephrine (NE) levels and activating NA metabotropic receptors, thereby suppressing the firing activity of cortical neurons.

In this study, the aim is to confirm the effect of stimulant medications, and their possible effects upon reversing the abnormal activity of primary neural populations in ADHD that was found in a previous study (Rowe et al., 2004a,c). Since stimulant medications are known to reduce the activity of the LC (Pliszka et al., 1996; Solanto, 1998), and the LC is known to stimulate the TRN (Destexhe et al., 1994; McCormick, 1989; Sherman and Guillery, 2001), it is predicted that stimulant medications will indirectly result in a reduction in intrathalamic activity involving the TRN. In a second hypothesis, given the affect of NA receptors upon reducing the activity of cortical neurons it is also predicted that stimulant medications will decrease the activity of cortical neurons, by increasing cortical NE levels, and activating NA receptors. A third hypothesis predicts a general decrease in dendritic response times, consistent with the reduced activity of inhibitory neurons and improved arousal. To test these hypotheses, the same biophysical model from prior EEG studies (Robinson et al., 2001b; Rowe et al., 2004a,b,c) is used to model tonic measures of EEG across multiple scalp sites before and after medication in 11 ADHD individuals, thereby providing values for key neurophysiological parameters in each condition.

2. Method

2.1. Overview of the model

The structure of the model is reflected in a modest number of neurophysiological parameters, which must lie within plausible physiological limits (Robinson et al., 2004). Variation outside these limits leads to high mismatch between model and experiment, and/or seizure like activity in the waveforms (Robinson et al., 2002). Such variations are thus not relevant to the clinical subjects of interest and are not considered here.

The model parameters appear in the expression for the theoretical EEG spectrum used in inverse modelling of experimental EEG data (Rowe et al., 2004b). For brevity the equations and numerical details have been omitted. These, including the complete methodology are summarized in Rowe et al. (2004b), while the full mathematical analysis is also given elsewhere (Robinson et al., 1997, 2001a,b). The physiological features used in the model have also been justified in previous studies (Rennie et al., 2002; Robinson et al., 1997, 2001a,b; Rowe et al., 2004b). In this study, the focus is on the ability of the model to provide physiological insight into tonic changes in EEG spectra due to stimulant medications, and whether the results are consistent with known physiology and the pharmacological effects of these drugs.

2.1.1. Neurophysiology—mass action—macroscopic approach

The neurophysiology of the model is shown in Fig. 1. Action potentials from various neurons, represented as