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Clinical Neurophysiology xx (2004) 1–12

www.elsevier.com/locate/clinph

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

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Accepted 2 August 2004

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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1388-2457/$30.00
doi:10.1016/j.clinph.2004.08.001

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

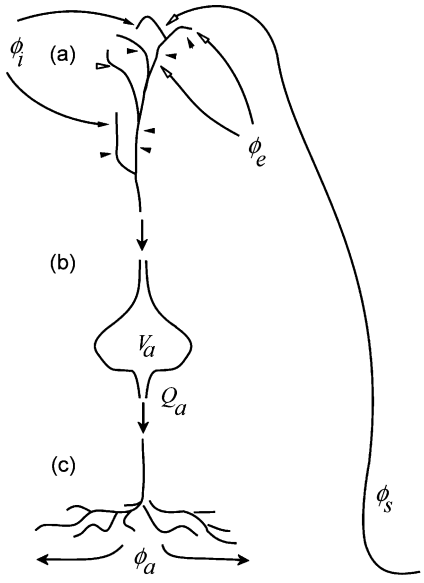

Fig. 1. The basic neuronal physiology incorporated by the EEG model is shown in a cortical neuron showing (a) synaptic connections at the dendritic tree originating from pulse-rate fields ϕ_b ($b=i,e,s$), (b) the somatic membrane potential V_a ($a=e,i$) at the cell body with resultant impulse firing rate Q_a, and (c) spread of action potentials as the field ϕ_a along axons.

neural pulse-rate fields $\phi_b=\phi_e,\phi_i,\phi_s$ (cortical excitatory, intracortical inhibitory, and TC relay, respectively) arrive at the dendritic tree (Fig. 1a) inducing perturbations in the membrane potential V_a, which varies according to the net effect of all inhibitory and/or excitatory inputs, including characteristic rate constants. The temporal spread and conduction delay of these signals within the dendritic tree are parameterized by the dendritic rate constants β and α, representing the typical rise and decay rates, respectively, of the soma response to incoming action potentials at the synapse. This is characteristic of the low-pass response characteristics of neurons including synaptic delays associated with receptor dynamics (Robinson et al., 2004).

The mean firing rate Q_a (or *pulse density*) of the neuron (Fig. 1b) is assumed to vary according to a typical nonlinear sigmoid function, such as that found in the McCulloch-Pitts neuron (Anderson, 1995; Fausett, 1994). The sigmoid relates the firing rate to the average membrane potential V_a, and resembles a smoothed step function (Freeman, 1975). However, if we treat the EEG signal as being due to small perturbations about a steady state, we can linearize the sigmoidal response by replacing it by its steady-state slope ρ_a and combining this with the number N_{ab} and response strength s_b of synapses to give the neural gains $G_{ab}=\rho_a N_{ab} s_b$ listed in Table 1 (Robinson et al., 1997, 2001b). These gains parameterize the differential number of neural pulses out per pulse in and describe the effect of input perturbations from the various afferent neural fields ϕ_b on the firing rate Q_a of excitatory and inhibitory neurons ($a=i,e$).

Action potentials propagate away from cells in a given region along multiple axons, forming average pulse density

Table 1
Typical parameter values for the EEG and electromyogram (EMG) theoretical model spectrum as described in text. The neural gains G_{ab} reflect the input/output response characteristics of the respective neural populations, while other parameters reflect dendritic and axonal delays, power normalization and filtering properties of the scalp. The EMG parameter A, independent of the EEG model, is a normalization factor, which corrects for pericranial muscle artefact according to an EMG algorithm

Model	Parameter	Description	Typical value
EEG Model	γ_e	Cortical damping rate (v/r_e)	130 s^{-1}
	α	Dendritic decay rate	75 s^{-1}
	β	Dendritic rise rate	4.0/α
	t_0	Conduction delay through thalamic nuclei and projections	0.084 s
	G_{ee}	Excitatory gain in pyramidal cells	5.4
	G_{ei}	Local intracortical gain (net inhibitory − stellate cells	−7.0
	G_{ese}	Cortico-thalamocortical gain via SRN	5.6
	G_{esre}	Cortico-thalamocortical gain via TRN	−2.8
	G_{srs}	Intrathalamic gain	−0.6
	$k_0 r_e$	Volume conduction filter parameter	3.0
	r_e	Characteristic pyramidal axon length	0.08 m
	P_0	Overall power normalization (μV^2/Hz)	Calculated from data
EMG	A	Power normalization	0.5 μV^2/Hz

fields ϕ_a (Fig. 1c). The potentials propagate at an average velocity $v_a=10$ m s^{-1} depending on axonal myelination (Bullier and Henry, 1979; Dinse and Kruger, 1994). The pulse density fields have reduced effects at greater distances due to decreasing terminal density. This effect is incorporated in the model via the damping rate $\gamma_a=v_a/r_a$, where r_a is the characteristic range of type a axons and v_a is the velocity (Jirsa and Haken, 1996; Robinson et al., 1997). This function is incorporated in a continuum approach, where the equations describe a continuum of points having the average properties of typical neurons, as described above. This also uses a two-dimensional continuum, which is justified by the relative thinness of the cortex and the scale of neural modelling and experimental measures (Robinson et al., 1997, 2001b).

2.1.2. Cerebral connectivity

The axonal range of intracortical inhibitory and excitatory stellate cells ($r_i \sim 0.1$ mm) is significantly shorter than the axons of pyramidal cells ($r_e \sim 80$ mm) and significantly smaller than the minimum scale of EEGs (10–50 mm for scalp recordings; Braitenberg and Schüz, 1991; Nunez, 2002). This permits two simplifications to the model equations: the inhibitory field ϕ_i can be taken as approximately equal to mean firing rate Q_i; and the time constant

$1/\gamma_i$ (very large γ_i), relating to the inhibitory fields, can be approximated by zero (Robinson et al., 1997, 2001b). A further simplification described in Robinson et al. (1997) is that on average the number of synapses are proportional to the number of neurons involved, and it is argued that $G_{ee} \approx G_{ie}$ and $G_{ei} \approx G_{ii}$.

The pyramidal cells, as well as having intracortical and corticocortical connections G_{ee}, also have subcortical projections (Fig. 2). Here, the various pathways have gains G_{ab}, where additional subscripts r and n refer to the TRN and external sources, respectively. The pyramidal cells ϕ_e synapse with thalamic relay nuclei (SRN, G_{se}), which then project to the cortex via ϕ_s (gain G_{es}). The total gain of this pathway $G_{ese} = G_{es}G_{se}$ is positive since it involves excitatory glutamatergic neurons. There is also a negative feedback pathway $G_{esre} = G_{es}G_{sr}G_{re}$ where corticothalamic collaterals synapse with the inhibitory TRN (gain G_{re}), which in turn projects to thalamic relay nuclei (G_{sr}), and back to the cortex. An intrathalamic loop, with overall gain $G_{srs} = G_{rs}G_{sr}$ is also present, comprising reciprocal connections between TC relay nuclei and the TRN. Both G_{srs} and G_{esre} are negative since the TRN consists of inhibitory GABAergic neurons. The axonal transmission through G_{ese} or G_{esre} also induces a signal delay time $t_0 \approx 0.085$ s, in addition to small delays from dendritic filtering. The activity of these gains, transmission delays, and dendritic filtering exert specific and interdependent effects on the spectral properties of the EEG (Rennie et al., 2002; Robinson et al., 2001b, 2002) and are used to interpret variance in the measures in this study.

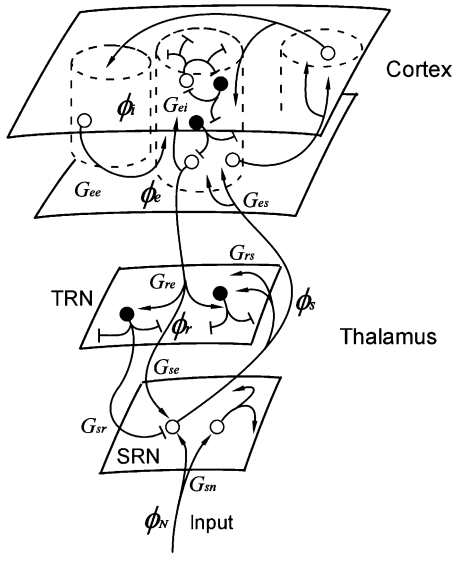

Fig. 2. Schematic of pathways and connections in the model, and their anatomical significance. Open circles represent excitatory neurons and inhibitory neurons are shown with solid circles. Long-range projections are depicted by solid arrows and short-range projections by bars. (i) Local intracortical loops are formed by inhibitory and excitatory stellate cells, and pyramidal types as G_{ei}, with the spatial extent of projections confined within the minicolumns (dashed). (ii) Corticocortical projections from pyramidal cells extend both locally and across the cortex as G_{ee}. (iii) These cells also project ϕ_e to the thalamus where signals may propagate via (a) the TRN then SRN with gain $G_{esre} = G_{es}G_{sr}G_{re}$, or (b) directly via SRN as gain $G_{ese} = G_{es}G_{se}$. (iv) TC afferents returning from the SRN project activity ϕ_s to the cortex as gain G_{es}. (v) Within the thalamus, intrathalamic loops $G_{sr}G_{rs}$ comprise reciprocal projections between the inhibitory TRN and excitatory SRN. (vi) Cortical activation or sensory input occurs via ϕ_N and ϕ_s with gain $G_{es}G_{sn}$. (vii) Additional small delays are induced by dendritic filtering.

2.1.3. Independent parameters

The preceding parameters with their typical parameter values are listed in column 4 of Table 1. These values were obtained from obtained from group averages of parameters generated from fits to eyes-closed spectra of 100 healthy controls during earlier previous experimental work (Robinson et al., 2004; Rowe et al., 2004b). The values serve as the initial parameter values at the commencement of the fitting procedure, and are consistent with independent sources and physiological measures (Nunez, 1995; Rall, 1967; Robinson et al., 1997, 2004; Shwedyk et al., 1977; Stulen and DeLuca, 1981; van Boxtel, 2001). Varying the initial parameter values before the fitting procedure has also been found to yield the same spectral fit and end parameter values to within their uncertainties[1] (Rowe et al., 2004a,b). Recent work by Robinson et al. (2004) using a Monte Carlo fitting routine on the same EEG model has also been found to produce nominal parameter values that are consistent with those found in Table 1, Rowe et al. (2004b).

Some parameters in Table 1 are independent of the spectral shape, but are important factors when simulating EEG. First, $k_0 r_e$ is a fixed parameter and is introduced to approximate the filtering of high spatial frequencies ($\geq k_0$) due to volume conduction by the cerebrospinal fluid, skull and scalp (Robinson et al., 2001b). The overall power normalization parameter P_0 (Table 1) is calculated from the experimental data and is related to the model parameters $G_{es}G_{sn}$, ϕ_n and r_e, and is adjusted during fitting according to the overall power of the experimental spectrum (Rowe et al., 2004b).

The electromyogram (EMG) power normalization parameter A is part of an EMG correction algorithm (Rowe et al., 2004b) that was developed from the EMG modelling work of van Boxtel (2001) and Shwedyk et al. (1977). During the fitting procedure the EMG parameter A is adjusted to correct for high frequency pericranial muscle artefact and does slightly effect the amplitude of the high frequency (>25 Hz) component of the spectra (Rowe et al., 2004b). This is consistent with observations by us and others of enhanced spectral power at high frequencies (>25 Hz) during conditions of jaw clenching, frowning, and other facial movements (Rowe et al., 2004b; Shwedyk et al., 1977; van Boxtel, 2001).

[1] This refers to the smallest possible change in a parameter for a given data set that will cause a significant deviation (or χ^2 error) between the theoretical and experimental spectra.

2.2. EEG data acquisition and scoring

EEG data were acquired using the recording protocol in Lazzaro et al. (1999). The focal recording sites of interest in this study were F3, C3, P3, Fz, Cz, Pz, F4, C4, and P4. During the recording subjects were awake and non-drowsy and EEGs were acquired continuously for 2 min during a resting eyes-closed condition. Ocular artefacts were corrected offline according to the method of Gratton et al. (1983). For each EEG recording the average experimental power spectrum P_{exp} from 0.24 to 49.8 Hz (204 data points) was calculated for 27 successive 4 s epochs using a fast Fourier transform analysis.

2.3. EEG data fitting

For model fitting, $\log_e$ of the sum P_{est} of the theoretical EEG and EMG spectra was fitted to $\log_e P_{exp}$ (experimental spectra) measured at a single site. Logarithms were taken to permit each frequency decade to be weighted roughly equally, thereby maintaining fits based on spectral detail rather than the number of data points (Rowe et al., 2004b). To minimize noise P_{exp} was also smoothed over a full width of 1.0 Hz, as this has been found to reduced uncertainty in the model parameters (Rowe et al., 2004b). The error between P_{est} and P_{exp} was reduced by parameter optimization using the Levenberg–Marquardt method (Press et al., 1992), in which

$$\chi^2 = \sum_{I=1}^{N} \frac{[\log_e(P_{exp}(f_i)) - \log_e(P_{est}(f_i))]^2}{\sigma_i^2}$$

was minimized (Rowe et al., 2004b).

The data fitting procedure was identical to those detailed in Rowe et al. (2004b), with the following exceptions: (i) a stopping criterion was set at $\chi^2 < 25$ to ensure a good fit, (ii) $\sigma_i = 0.2$ was assumed on the basis of relatively even fluctuations in $\log P(f)$ versus frequency, and (iii) γ_e was constrained within the limits $5210\ s^{-1}$. Previous work implied that γ_e should be within this range since 89% of values for γ_e converged within these limits, 8% converged within the following broader limits, $210 < \gamma_e < 400$ or $35 < \gamma_e < 50$, and only 3% failed to converge (Rowe et al., 2004b). Furthermore, axonal velocity of myelinated neurons in the mammalian cortex is also expected to be within $10\ m\ s^{-1}$ (Bullier and Henry, 1979; Dinse and Kruger, 1994), and axonal range r_e within 0.00.1 m (Braitenberg and Schüz, 1991; Nunez, 1981). Therefore, given $\gamma_e = v_e/r_e$, broad limits of $5–210\ s^{-1}$ for γ_e can be determined that approximate experimental findings (Rowe et al., 2004a,b).

3. Subjects

EEG recordings were obtained from 11 adolescent males diagnosed with ADHD (mean age = 14.1 years; SD = 1.5; age range = 12–17 years) with the appropriate ethical clearances and informed consent (Lazzaro et al., 1999). All subjects were required to have had no history of neurological disorder or substance abuse. The patients were referred by pediatricians, clinical psychologists and psychiatrists who considered them to have a diagnosis of ADHD. All patients were further categorized according to DSM-IV criteria (APA, 1994) using a semi-structured interview (Lazzaro et al., 1999). Most subjects were of the Combined Type, one subject was predominantly Hyperactive-Impulsive Type and another was predominantly Inattentive Type. These subjects were included to maintain experimental power, although additional analysis is provided without these subjects in the results section.

In the unmedicated condition, subjects were withdrawn from stimulant treatment for a period of 2 weeks or longer prior to testing. At this time each patient was rated using the Conners' Parent (48-item) and Conners' Teacher (28-item) Rating Scales (Conners, 1989), and the Achenbach Child Behavior Check List for parents (Achenbach, 1991a) and Teacher's Report Form (Achenbach, 1991b). Subjects were included in the study where their measures deviated 1.5 SDs above published norms for the Conners' Teaching Ratings and 1.0 SDs above the norm for the Conners' Parent Rating. The subjects were also evaluated for intellectual ability using the assessment protocols described in Lazzaro et al. (1999, 2001) and were required to have an IQ estimate of 75 or greater.

After the initial EEG testing, subjects recommenced medication and then returned for EEG recordings 1–2 months later while still on stimulant medication; 7 were being prescribed Dextroamphetamine, 4 Methylphenidate. Dosage was of a typical amount for the treatment of ADHD with a dosage of 130 mg daily in divided doses and medication was administered 1 h prior to recordings.

3.1. EEG data acquisition and scoring

The EEGs at various sites were acquired as part of a battery of electrophysiological tests using the same recording protocols as in Lazzaro et al. (1999). The focal recording sites of interest in this study were F3, C3, P3, Fz, Cz, Pz, F4, C4, and P4. During the recording, subjects were awake and non-drowsy with EEGs acquired continuously for 2 min during a resting eyes-closed condition. Ocular artefacts were corrected offline according to the method of Gratton et al. (1983). For each EEG recording the average experimental power spectrum P_{exp} from 0.24 to 49.8 Hz (204 data points) was calculated for 27 successive 4 s epochs using a Fast-Fourier transform.

4. Results

4.1. Quantitative EEG (qEEG) analyses

Relative and absolute qEEG power in the Delta (1.25–3.5 Hz), Theta (3.5–7.5 Hz), Alpha (7.5–12.5 Hz), and Beta

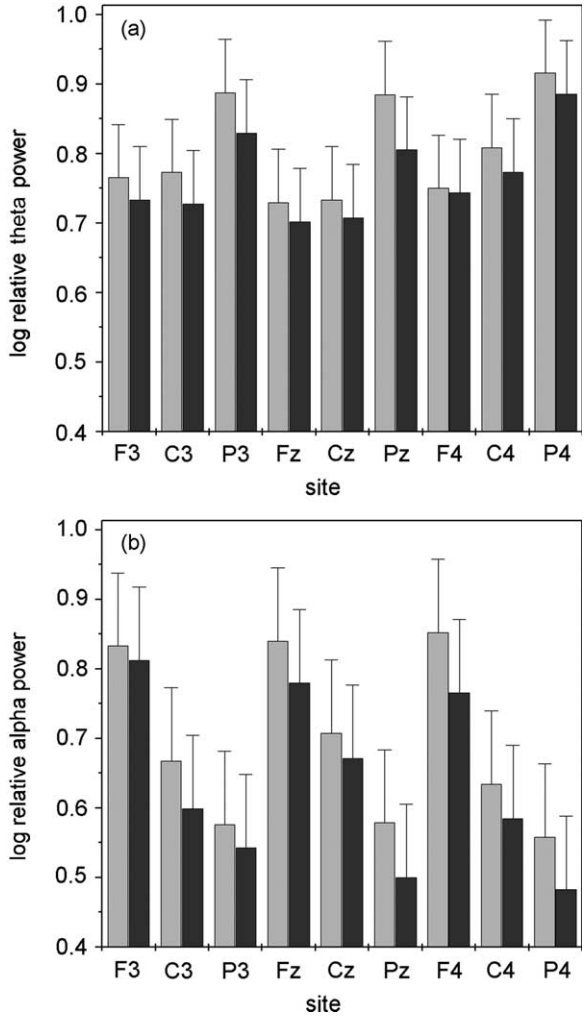

Fig. 3. Mean values of power calculations ($\log_{10}$; +2 standard error, SE, bar) across scalp site are shown for (a) relative theta power and (b) relative alpha power. The light grey bars represent the unmedicated condition and the dark grey bars represent the medicated condition.

(12.5–25.0 Hz) bands were computed for each subject across site and condition. Since the focus of this study are the physiological model parameters, for brevity full details and discussion of the qEEG analysis and results has been omitted, as similar studies are described in references. However, the statistical procedure follows the same method as the Model parameter analyses and data screening section, as described below, with the exception of log transformation of the data. A summary of the qEEG results is provided to show changes due to medication and to permit comparison with ADHD subjects from other studies. Although, there were no significant results, possibly due to the small sample size, there was a trend showing a reduction in relative theta and alpha power in the medication condition, as shown in Fig. 3(a) and (b), which was significant ($P<0.05$) using an independent samples ANOVA.

4.2. Model parameter analyses and data screening

In Fig. 4, two examples chosen at random illustrate the high accuracy of the model fits obtained for most subjects. The model is shown to closely match the characteristic spectral properties of the EEG, and with such spectra the model provided robust parameter values.

In a limited number of cases (see below), outliers occurred where spectra did not contain sufficient information to fit the complete set of physiological parameters accurately, possibly due to noise and/or featureless spectra. These cases had very wide basins (flat valleys) of attraction in parameter space, which caused parameters to be widely scattered, with some values becoming abnormally large. Following the convention in brain imaging studies, outliers ($\sim$8% of data points) were accounted for by removing outlying data points (median $\pm$2.0 SD or more) in parameters of interest, α, G_{ei}, G_{ee}, G_{ese}, G_{esre}, and G_{srs} and replacing these with the new mean. Each parameter was then submitted separately to a 2×9 way analysis of variance with variables referring to repeated-within-subjects factors: Condition (unmedicated vs. medicated), and Site (F3, C3, P3, Fz, Cz, Pz, F4, C4, and P4). As the central focus of this study was medication effects, main effects of site were not analysed. Significant effects were also explored further with simple effects analysis using the nonparametric paired-samples Wilcoxon Signed Ranks Test, given the small sample size.

Of particular interest were parameters G_{srs}, G_{ei}, G_{ee} and α. In a prior study, these gains were found to be abnormally high, and the dendritic response time α was abnormally low

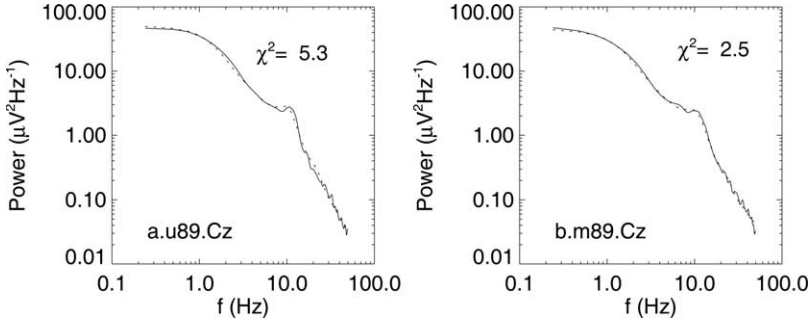

Fig. 4. Sample of model fits for one subject selected at random for the eyes-closed state at site Cz showing spectral data and fits for (a) unmedicated versus (b) medicated conditions. Each frame compares the subject's experimental spectra (–) with his modelled spectra (···), and lists the subject's ID number, site, and corresponding χ^2 value that reflects goodness of fit.

in unmedicated ADHD subjects (Rowe et al., 2004a,c). Significant effects of medication for each parameter (with the exception of G_{ei}) were found that were consistent with a reversal of the effects found in the prior study, and the hypotheses stated in the introduction.

Intrathalamic gain G_{srs}. A trend indicating a general reduction in the value of $|G_{srs}|$ across most sites, due to the effect of medication, was found (Fig. 5a) with $F_{1,10}=4.40$, $P=0.06$, $MS_e=0.30$. At two sites the mean of $-G_{srs}$ is a small negative that is consistent with zero to within uncertainties. Closer analysis of this result reveals significant simple main effects at sites Fz ($Z=-2.84$, $P<0.005$) and F4 ($Z=-2.3$, $P<0.05$) due to the effect of medication. The reduction in $|G_{srs}|$ at site C3 (Fig. 5a) was also worth noting ($Z=-1.87$, $P=0.06$).

Intracortical gain G_{ei}. Fig. 5b shows that there was a general reduction in intracortical gain $|G_{ei}|$ at the most sites in the medication condition; however, these effects were not significant.

Corticocortical gain G_{ee}. Fig. 5c shows that there was a significant main effect of medication ($F_{1,10}=5.77$, $P<0.05$, $MS_e=11$) for corticocortical gain G_{ee}, with reduced gain at the most sites in the medication condition.

Dendritic response time $1/\alpha$. Fig. 5d shows that the dendritic response rate α was generally higher at frontal and central sites in the medication condition, consistent with a significant medication×site interaction ($F_{8,80}=2.26$, $P<0.05$, $MS_e=239$), and significant simple main effects at sites Fz ($Z=-2.13$, $P<0.05$) and C4 ($Z=-2.84$, $P<0.005$), some what coincident with the simple main effects for $|G_{srs}|$.

No other significant effects were found at the $P=0.05$ level; however, values of the remaining parameters were within normal limits, as found in a previous study examining values for ADHD subjects and their age- and sex-matched controls (Rowe et al., 2004a).

ADHD subtypes. The above analysis was also completed for the ADHD combined group without the two subtypes. In this analysis the pattern of results remained the same with simple effects indicated at F4 ($Z=-2.19$, $P<0.05$) and Fz ($Z=-2.55$, $P<0.05$) for $|G_{srs}|$, a general reduction in $|G_{ei}|$, a significant main effect for G_{ee} ($F_{1,8}=5.51$, $P<0.05$, $MS_e=15$), and a significant medication×site interaction for α ($F_{8,64}=2.49$, $P<0.05$, $MS_e=183$). This suggests the medication affects on the EEG model in this study were not particularly sensitive to the ADHD subtypes, although this may be due to the small sample size.

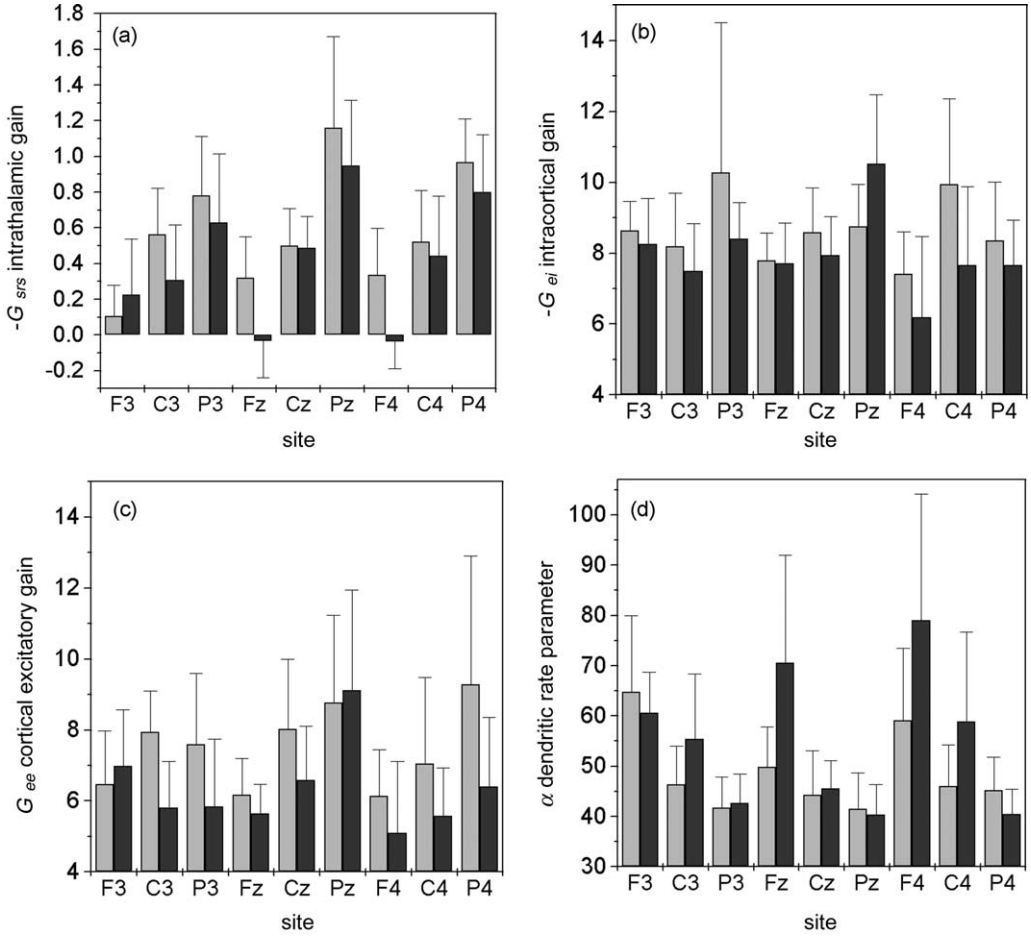

Fig. 5. Mean values (+2 standard error, SE, bar) across site for parameters: (a) G_{srs}, (b) G_{ei}, (c) G_{ee}, and (d) α showing a general reduction in cortical and intrathalamic gains, and increase in α at specific sites due to the effect of condition; unmedicated (light bar) and medicated (dark bar).

Medication type. The effect of medication type was assessed by repeating the same analysis on the full 11 subjects, except with medication type (Dextroamphetamine versus Methylphenidate) entered as a covariate. In this analysis medication type was not found to significantly covary with any of the above model parameters.

5. Discussion

In this study a biophysical model of brain activity based on primary neural properties, cell populations, and networks, has been used to infer physiological differences underlying tonic EEG changes in 11 ADHD subjects before and after treatment with stimulant medication. The results confirm the hypotheses listed in the introduction and show that the model was able to significantly discriminate the effect of stimulant medication according to the following parameters: (i) a decrease in intrathalamic gain $|G_{srs}|$ involving the TRN, consistent with the first hypothesis, (ii) a decrease in the gain of excitatory pyramidal cells G_{ee}, consistent with the second hypothesis (although a comparable significant decrease in the gain of local stellate cells $|G_{ei}|$ was not found, see below), and (iii) a decrease in the dendritic response time $1/\alpha$, consistent with the third hypothesis.

The effect of $|G_{srs}|$, G_{ee}, and α was also localized towards frontal and central sites (Fig. 5a), consistent with studies showing abnormal delta–theta EEG activity primarily at similar scalp regions (Lazzaro et al., 1999), and suggestions of frontal and executive function abnormalities (Barkley, 1997). These results suggest that the effect of stimulant medication upon intrathalamic activity $|G_{srs}|$, cortical (pyramidal) excitatory activity, and synapto-dendritic response times α may lead to an improvement in frontal lobe activity, as a result of reduced G_{ee}, $|G_{srs}|$, higher α, and improved cortical arousal and/or signal processing. This is consistent with a prior suggestion that individuals with ADHD may suffer dysfunctional neural activity in specific cortical networks rather than diffuse dysfunction throughout the entire cortex (Rowe et al., 2004a,c). More extensive work on analysing topographical effects of neurophysiological parameter variations as a result of medication in ADHD subjects will elucidate this finding.

In the previous study, applying the same methodology to a sample of 54 unmedicated ADHD subjects, the results indicated that patients differed significantly from their healthy controls in terms of three physiological parameters: increases in inhibitory intrathalamic gain $|G_{srs}|$, intracortical gain $|G_{ei}|$, and a decrease (slowing) of the dendritic response rate α (Rowe et al., 2004a,c). These neurophysiological differences were suggested to indicate: (i) a state of hypoarousal due to increased intrathalamic activity $|G_{srs}|$ involving the TRN. This activity is associated with increased delta–theta power, and characteristic of reduced arousal states and sleep. (ii) Interference of sensory processing due to increased intracortical activity generated primarily by local inhibitory stellate cells $|G_{ei}|$. (iii) A slowing of dendritic responses, activity that is consistent with reduced arousal, and slower GABA receptor activity (e.g. $GABA_B$), and the increased gain of inhibitory neurons in the cortex $|G_{ei}|$ and the thalamus $|G_{srs}|$ (Rowe et al., 2004a,c). Therefore, the effect of stimulant medication on reducing $|G_{srs}|$ and increasing α is consistent with reversing the abnormal high activity of $|G_{srs}|$ and low value of α found previously in unmedicated ADHD subjects. There was also a trend illustrating a reduction in $|G_{ei}|$ due to medication (Fig. 5), consistent with the reversal of the abnormally high value found in Rowe et al. (2004a,c), although this effect was not statistically significant it is discussed in more detail below. Finally, there was also a trend suggesting that these effects may be associated with a reduction in theta and alpha power due to medication (Fig. 3), the former consistent with the findings of theta normalization in previous studies (Clarke et al., 2002a, 2003; Loo et al., 1999; Lubar et al., 1999).

5.1. Intrathalamic activity and arousal

The reduction in intrathalamic gain $|G_{srs}|$ involving the TRN is consistent with the proposed effects of stimulant medication upon improving arousal. Stimulant medications are thought to *decrease* the baseline tonic firing of the LC via metabotropic α-2 receptors, which reduce neurotransmitter release in their target neurons (Curet et al., 1992; Graham and Aghajanian, 1971; Lacroix and Ferron, 1988), similar to the effects of Clonidine (Pliszka et al., 1996). This can lead to a reduction in the tonic stimulation of the TRN by LC afferents, given this effect outweighs the direct effect of extracellular NE (due to stimulants) upon increasing TRN and TC relay activity (McCormick, 1989). In turn, decreased TRN activity leads to less inhibition (hyperpolarization) of TC cells (Steriade and Amzica, 1998; Timofeev et al., 1996). This is characteristic of increased arousal states, where TC cells become more depolarised and TRN cells become more hyperpolarized (Steriade, 2000). Increased activity in TC circuitry (gain G_{ese}) and reduced activity via the TRN (gain G_{esre}) can also lead to an increase in alpha and beta activity (Robinson et al., 2001b; Rowe et al., 2004b). In contrast, during drowsiness and the early stages of sleep, the activity of the TRN increases leading to the hyperpolarization (inhibition) of TC relay cells via inhibitory GABAergic projections from the TRN (Steriade and Amzica, 1998). This switches the firing mode of TC relay cells to a *burst* or *oscillatory* mode, which gates the input of stimuli (Domich et al., 1986). The interaction of the TRN via the intrathalamic circuit G_{srs} and input from corticothalamic collaterals G_{esre} can lead to the generation of *spindle* oscillations in the EEG (Bal et al., 1995; Contreras et al., 1996a; Steriade et al., 1987). Further hyperpolarization of TC cells by the TRN during sleep eventually leads to enhanced delta–theta oscillations

(Amzica and Steriade, 1998; Destexhe and Sejnowski, 2002; Dossi et al., 1992).

It is possible that the above neural mechanisms are also involved in the reduction of arousal and the delta–theta enhancements in ADHD subjects, consistent with suggestions of corticothalamic hypoarousal in ADHD (Barry et al., 2003; Defrance et al., 1996; Satterfield and Cantwell, 1974). As mentioned, previous findings have also found increased intrathalamic $|G_{srs}|$ and inhibitory gains $|G_{ei}|$, but lower dendritic response rates α (larger time constants) in ADHD subjects (Rowe et al., 2004a,c). Other results have indicated that intrathalamic activity was also associated with delta–theta enhancements (Rowe et al., 2004b), reduced arousal and sleep states (Robinson et al., 2001b). Increased activity of the inhibitory $GABA_B$ receptors is also consistent with lower dendritic response rates, compared with faster AMPA receptors of excitatory neurons (Thomson, 1997; Thomson et al., 1996). These $GABA_B$ receptors, in particular, are known to become increasingly active during reduced arousal states, particularly in the thalamus, but also in the cortex (Contreras et al., 1996b; Juhasz et al., 1994; Kim et al., 1997). In summary, stimulant medications could well act to suppress the activity of the TRN, thereby increasing thalamocortical and synaptic activity.

5.2. Cortical activity, norepinephrine (NE) and dopamine

Stimulant medication is known to influence the NA and DA systems, resulting in changes in the activity of other primary neural populations, which are modulated by these secondary systems (Plizka, 2000; Solanto, 1998). In particular, increased activity of the LC during aroused states (Berridge and O'Neill, 2001; Trulson and Jacobs, 1979) is thought to reduce the activity of cortical neurons via α-2 metabotropic NA receptor mechanisms (Curet et al., 1992; Hasselmo et al., 1997; Segal and Bloom, 1976). This would suggest that increased extracellular NE levels due to the administration of stimulant drugs would enhance this process by increasing NA receptor activation. Consistent with the current results showing a significant reduction in the gain G_{ee} of long range pyramidal cells due to the effect of medication, but not local stellate cell populations $|G_{ei}|$.

In addition to NA effects, stimulant medications are also known to act as indirect agonists on dopaminergic neurons. This can also lead to the suppression of pyramidal cells G_{ee} in layer V of the prefrontal cortex via the activation of metabotropic D2 receptors (Gulledge and Jaffe, 2001; Volkow et al., 1997). Consistent with this studies, significant findings for reduced G_{ee} at frontal and central sites, rather than parietal ones. It appears some DA and NA agonists may preferentially target DA and NA receptors on pyramidal rather than stellate cells (Gulledge and Jaffe, 1998), and in some cases DA activation can lead to an increase in the activity of interneurons, particularly inhibitory stellate types (Gonzalez-Islas and Hablitz, 2001; Seamans et al., 2001). This may explain why there was not a significant reduction in $|G_{ei}|$ due to the effect of medication, although a significant increase may have been expected.

It is possible that the design of this study was not powerful enough to detect a significant change in the parameter $|G_{ei}|$. In the previous study using unmedicated subjects with identical diagnoses, $|G_{ei}|$ was abnormally high, and the sample size ($n=54$) was much larger (Rowe et al., 2004a,c). Alternatively, the NA and DA activating stimulant medications used in this study may not significantly alter the activity of these local stellate cell types, instead having a greater effect on long range pyramidal cells and subcortical arousal networks involving the LC and TRN. As discussed in the following section, the cholinergic system may be more prominent in modulating the activity of these local circuit neocortical networks. Other more NA receptor specific drugs which target these local neuronal types may also be required.

5.3. Intracortical activity and acetylcholine

The above results suggest that other mechanisms may also account for and/or contribute to cortical abnormalities in ADHD. Recent evidence suggests that individuals with ADHD may have abnormalities in the cholinergic system (Biederman and Spencer, 2000). This system uses acetylcholine (ACh) and other ligands to modulate various excitatory (e.g. AMPA, NMDA) and inhibitory (GABA) processes throughout the cortex. Nicotine, which activates cholinergic nicotinic ACh receptors (nAChRs), has been found to improve symptoms in individuals with ADHD (Conners et al., 1996; Levin, 2002), and a strong association has been found between ADHD diagnosis and nicotine intake (Milberger et al., 1997; Pomerleau et al., 1995; Tercyak et al., 2002). The administration of acetylcholinesterase inhibitor Donepezil (Aricept®, an ACh agonist) in youths (8–17 years) with ADHD has also shown improvements in symptoms (Wilens et al., 2000).

In a previous study it was hypothesized that a hypoactivity of the cholinergic system could lead to abnormal cortical activity in ADHD subjects (Rowe et al., 2004a). Reductions in the activity of this system is also known to lead to the disinhibition of the TRN due to deactivation of M2 muscarinic receptors (Hu et al., 1989; McCormick and Pape, 1988; Sato et al., 1987), and is considered an important mechanism of reduced arousal states and slow wave sleep including delta-theta activity (Rowell et al., 2003). Similar muscarinic receptor types sensitive to ACh have also been shown to suppress the activity of cortical interneurons (stellate cells), and this has been suggested as a mechanism that improves signal processing activities in cortical circuits (Hasselmo and Fehlau, 2001; Koós and Tepper, 2002; Murakoshi, 1995). In contrast, in response to TC input, nAChRs are found to enhance the activity of TC neurons and their afferent terminals in layer IV of the neocortex where local stellate cells G_{ei} are particularly dense and pyramidal cells are

absent (Gil et al., 1997; Kimura et al., 1999; Lambe et al., 2003). Thus, through increased ACh, the cholinergic system decreases intrinsic cortical activity, but enhances external inputs that are transmitted via TC projections. Therefore, specific cholinergic agonists, rather than NA ones (including stimulants), may serve as better pharmacological agents for improving signal processing in local cortical circuits, while NA agonists may be more specific to improving cortical arousal. However, due to the diffuse and strong effects of cholinergic agonists on cortical activity (Sarter and Bruno, 1997; Zaborszky, 2002), future research will need to focus on pharmacological agents that bind specific subtypes of nicotinic and muscarinic receptor types (Dani, 2001; Zeng and Wess, 2000) to prevent adverse side effects. Similarly, newer NA based medications such as atomoxetine (Strattera®), which affect more specific receptor subtypes may be found to better target neural populations such as local circuit neurons and those in the frontal lobes that are thought to be involved in executive functions.

6. Conclusion

A biophysical model of the brain has been recently developed that has been successfully used to fit EEG spectra from 11 ADHD subjects before and after treatment with stimulant medication. The change in the EEG as a result of this medication is characterized by a reduction in intrathalamic gain $|G_{srs}|$ involving the TRN, a reduction in excitatory gain G_{ee}, and a decrease in dendritic response times $1/\alpha$. The effects for $|G_{srs}|$ and α are consistent with a prior study which shows an abnormal increase in $|G_{srs}|$ and an increase in $1/\alpha$ in ADHD subjects with similar diagnosis, and is suggested to provide evidence for corticothalamic hypoarousal. Therefore, stimulant medications may improve corticothalamic arousal in ADHD subjects by modulating subcortical arousal networks involving the TRN, and synapto-dendritic activity in the cortex. The mechanism underlying the reduction in $|G_{srs}|$ has been suggested to occur due to the suppression of LC activity via α-2 NA metabotropic receptor activation. This in turn reduces the tonic stimulation of the TRN by the LC, thereby reducing inhibitory actions upon TC activity. Similarly, the reduction in G_{ee} has been suggested to occur due the suppressive effects of NA and DA receptors on pyramidal cells.

Other cortical abnormalities have also been proposed in ADHD. In particular, a hypoactivity of the cholinergic system can account for increased activity in intracortical neurons due to a deactivation of mAChRs. These receptor types are normally activated in response to cholinergic activity, thereby suppressing the firing of intracortical neurons and possibly reducing cortical noise and/or spurious neural activities. These results suggest that individuals with ADHD may have abnormalities in both the cholinergic and noradrenergic systems, and the effects of these systems may be interdependent. NA antagonists such as dextroamphetamine and methylphenidate can improve arousal by reducing the tonic firing of the LC, thereby reducing the tonic inhibitory action of the TRN. In contrast, cholinergic agonists such as donepezil and ACh can activate mAChRs and nAChRs. The mAChRs can suppress intracortical circuits, as well as suppressing the activity of the TRN, while the nAChRs can enhance TC inputs, possibly functioning as a mechanism which increases signal-to-noise ratio in the cortex.

Of final note is that the sample size used in this study is relatively small and a more powerful design, which differentiates subtypes may lead to more significant effects and additional diagnostic information. The use of a double-blind placebo experimental design would also provide better confirmation of the existing results. Despite this, significant effects have been found which are consistent with the model's theoretical predictions and prior results, as well as independent theoretical and experimental studies. This has provided encouraging support for the approach and the design of similar future studies that can complement more microscopic techniques, thereby providing links between local and global physiological mechanisms. Future studies using this methodology may best examine the effects of both NA and cholinergic drug agents in larger samples of ADHD subjects and healthy controls participating in experimental paradigms measuring both baseline (tonic) cortical activity and neural flexibility in response to event-related (phasic) stimulus paradigms.

Acknowledgements

We would like to acknowledge the valuable contribution of Sean Kristofferson who collected the database of ADHD subjects. This research was funded by the Australian Research Council and Postgraduate Awards from the Faculty of Medicine, University of Sydney, and the Westmead Millennium Foundation, Westmead Hospital.

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