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BIOPHYSICAL MODELING OF TONIC CORTICAL ELECTRICAL ACTIVITY IN ATTENTION DEFICIT HYPERACTIVITY DISORDER

D. L. ROWE

School of Physics
University of Sydney
New South Wales, Australia

and

Brain Dynamics Centre & Dept. of Psychological Medicine
Westmead Hospital & University of Sydney
New South Wales, Australia

and

The Brain Resource Company
Sydney, New South Wales, Australia

P. A. ROBINSON

School of Physics
University of Sydney
New South Wales, Australia

and

Brain Dynamics Centre & Dept. of Psychological Medicine
Westmead Hospital & University of Sydney
New South Wales, Australia

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Address correspondence to Donald Rowe, School of Physics, University of Sydney, New South Wales, 2006, Australia. E-mail: drowe@physics.usyd.edu.au

I. L. LAZZARO

Brain Dynamics Centre & Dept. of Psychological Medicine
Westmead Hospital & University of Sydney
New South Wales, Australia

R. C. POWLES

School of Physics
University of Sydney
New South Wales, Australia

E. GORDON

Brain Dynamics Centre & Dept. of Psychological Medicine
Westmead Hospital & University of Sydney
New South Wales, Australia

and

The Brain Resource Company
Sydney, New South Wales, Australia

L. M. WILLIAMS

Brain Dynamics Centre & Dept. of Psychological Medicine
Westmead Hospital & University of Sydney
New South Wales, Australia

and

School of Psychology
University of Sydney
New South Wales, Australia

Psychophysiological theories characterize Attention Deficit Hyperactivity Disorder (ADHD) in terms of cortical hypoarousal and a lack of inhibition of irrelevant sensory input, drawing on evidence of abnormal electroencephalographic (EEG) delta–theta activity. To investigate the mechanisms underlying this disorder a biophysical model of the cortex was used to fit and replicate the EEGs from 54 ADHD adolescents and their control subjects. The EEG abnormalities in ADHD were accounted for by the model's neurophysiological parameters as follows: (i) dendritic response times were increased, (ii) intrathalamic activity involving the thalamic reticular nucleus (TRN) was increased, consistent with enhanced delta–theta activity, and (iii) intracortical activity was increased, consistent with slow wave (<1 Hz) abnormalities. The longer dendritic response

time is consistent with the increase in the activity of inhibitory cells types, particularly in the TRN, and therefore reduced arousal. The increase in intracortical activity may also reflect an increase in background activity or cortical noise within neocortical circuits. In terms of neurochemistry, these findings may be accounted for by disturbances in the cholinergic and/or noradrenergic systems. To the knowledge of the authors, this is the first study to use a detailed biophysical model of the brain to elucidate the neurophysiological mechanisms underlying tonic abnormalities in ADHD.

Keywords arousal, locus coeruleus, noise, norepinephrine, thalamic reticular nucleus, thalamocortical

INTRODUCTION

A large body of research has sought to determine whether the diagnostic category of Attention Deficit Hyperactivity Disorder (ADHD; APA, 1994) is distinguished by specific neural abnormalities. The most robust observation has been an abnormal increase of global delta–theta neural activity (Chabot & Serfontein, 1996; Clarke et al., 2001b; Lazzaro et al., 1999; Matsuura et al., 1993), indexed via electroencephalographic (EEG) recording. The results from these studies have been interpreted as an indication of cortical hypoarousal (Satterfield & Cantwell, 1974; Satterfield & Dawson, 1971), which has been further supported by measures of reduced skin conductance in ADHD subjects (Hermens, 2003; Lazzaro et al., 1999; Satterfield & Dawson, 1971). Consistent with the hypoarousal theory, stimulant medications, used as the primary form of treatment in ADHD, have been found to improve symptoms, particularly in subjects showing enhanced delta–theta activity and reduced skin conductance (Chabot & Serfontein, 1996; Clarke et al., 2002; Satterfield & Cantwell, 1974). Individuals with ADHD also show attentional deficits on cognitive tasks involving the extraction of relevant signals from background "noise" (Biederman & Spencer, 1999). This deficit may reflect an underlying abnormality in arousal (Biederman & Spencer, 1999; Yerkes & Dodson, 1908) or a primary breakdown in the mechanisms of selective attention and signal processing (Pliszka et al., 1996; Volkow et al., 2001).

Proposals concerning the neural mechanisms underlying hypoarousal in ADHD have focused on the locus coeruleus (LC) (Aston-Jones et al., 1999; Solanto, 1998). This nucleus is the primary source of noradrenergic (NA) fibers with widespread projections throughout the cortex (Berridge & Waterhouse, 2003), and the firing activity in these fibers increases in proportion to arousal level and decreases monotonically with the onset of sleep (Gottesmann, 2002a;

Trulson & Jacobs, 1979). It has been hypothesized that overactivity of the LC may underlie cortical dysfunction in ADHD (Konrad et al., 2003; Pliszka et al., 1996; Solanto, 1998), given that stimulant medications act to suppress LC activity via metabotropic α-2 receptors (Curet et al., 1992; Graham & Aghajanian, 1971; Ramirez & Wang, 1986). These drugs are also thought to increase extracellular norepinephrine (NE) and dopamine levels by blocking reuptake (Solanto, 1998). These studies suggest the direct effect of stimulant medication is to increase extracellular NE levels, whereas the indirect effect is to decrease intracellular NE levels in LC terminals. However, the precise physiological mechanisms in which these drugs modulate cortical activity and arousal remain unclear.

Recent work on biophysical modeling has focused on the role of the thalamocortical (TC) circuitry in the generation of neural activity across various states of arousal (Robinson et al., 2001b; Rowe et al., 2004c). Notably, this circuitry, which involves the thalamic reticular nucleus (TRN), has been shown to generate delta and theta activity (Robinson et al., 2001b; Rowe et al., 2004c; Steriade, 1999), and may be responsible for the delta–theta abnormalities in ADHD (Rowe et al., 2004a, 2004b). Numerous studies have also implicated the TRN in the modulation of arousal (e.g., Sherman & Guillery, 2001; Steriade et al., 1986). During reduced arousal and early stages of sleep, the firing activity of inhibitory neurons in the TRN increases (Contreras et al., 1996; Kim et al., 1997; Terman et al., 1996), inhibiting TC relay cells (Kim et al., 1997; Steriade et al., 1986). Such inhibition leads to significant changes in the activity of cortical neurons and the resultant EEG, including enhancement of delta–theta activity (Dossi et al., 1992; Robinson et al., 2001b; Steriade, 1999).

During increased arousal, the tonic firing activity of LC neurons increases (Rasmussen et al., 1986; Reiner, 1986). Many studies have found that these neurons can also increase the firing rate of inhibitory neurons in the TRN (Destexhe & Sejnowski, 2002; Sherman & Guillery, 2001), thereby indirectly exerting inhibitory effects on TC relay neurons. Overactivity of the LC in ADHD may therefore lead to over-stimulation of the TRN, potentially pushing these individuals closer to a state of cortical activity that is characteristic of high inhibitory TRN activity, leading to reduced cortical arousal and increased delta–theta activity. This process would also interfere with the relay of internal and external neural information via the TC relay neurons. Rapid information transfer requires rapid tonic firing of TC relay neurons, which closely follows incoming stimuli (Fanselow et al., 2001; Sherman, 2001). However, a tonic increase in TRN activity is likely to interfere with this relay process, due to an over-inhibition of the relay neurons.

Deficits in the processing of inputs relayed via the TC projection system

may also occur in the recipient cells residing in local cortical networks, and abnormalities in these local neural populations may also underlie the signal-to-noise breakdowns observed in ADHD. This is thought to involve a deficit in the successful processing of relevant stimuli from irrelevant or background stimuli, which receives a similar level of attention. Assuming that high-level information processing and integration occurs within local neural populations (Gibson et al., 1999; Gupta et al., 2000; Porter et al., 2001), it might be expected that most sources of noise relevant to such processes would originate primarily from large populations of local stellate interneurons (both inhibitory and excitatory), rather than long-range excitatory pyramidal types. These local circuit neurons, particularly inhibitory types, are thought to form important feed-forward inhibitory processes in response to TC input (Gibson et al., 1999; Gupta et al., 2000; Porter et al., 2001) and it has been suggested that they are involved in the sculpting and coordination of activities in their recipient neurons (Galarreta & Hestrin, 2001; Gupta et al., 2000). These interneurons also form the majority of synaptic connections within local neocortical circuits, and significantly outnumber those from the important TC inputs (Douglas et al., 1995; Gil et al., 1999; Zador, 1999). Therefore, it has been suggested that the effective processing of sensory information relayed via TC inputs requires a broad, *tonic* suppression of these local interneurons (Kimura & Baughman, 1997; Oldford & Castro-Alamancos, 2003). In this regard, noise intrusion in ADHD may be due to a deficit in the tonic suppression of local interneurons, which leads to an increase in neural chatter and/or neural activities in response to spurious or "background" TC inputs.

These signal processing deficits due to intrinsic cortical noise may also be related to the neural mechanisms of cortical hypoarousal (Biederman & Spencer, 1999; Yerkes & Dodson, 1908); that is, increased "noise" due to enhanced activity of the local circuit inhibitory interneurons may inhibit potential information processing activity of excitatory cortical neurons and create a state of cortical hypoarousal. This is consistent with the increased activity of GABAergic neurons during reduced arousal and sleep (Gottesmann, 2002b), particularly in the subcortex and inhibitory interneurons (TRN) of the thalamus (Thomson et al., 1996; Thomson, 1997), although the activities of these neurons in the neocortex is less clear (Borg-Graham, 2001). The sedative and anxiolytic effects of benzodiazepines and barbiturates, and anesthetics such as halothane and isoflurane are also known to (at least in part) produce these effects through marked potentiation of GABA responses in the cortex (Farrant, 2001). These studies suggest an increase in GABAergic responses may also be responsible for arousal and information processing abnormalities in ADHD.

The aim of this study was to provide a more precise quantification of the neural mechanisms underlying tonic cortical abnormalities in ADHD using a biophysical model of neural activity, developed to quantify the mechanisms of ongoing EEG activity (Rennie et al., 2002; Robinson et al., 2001b; 2004; Rowe et al., 2004c). The neurophysiological basis of the model has enabled an understanding of changes in cortical activity in terms of realistic physiological parameters (Robinson et al., 2001b; 2004). In particular, this has included the values of neurophysiological parameters underlying varying states of arousal (Robinson et al., 2001b; 2002) and the theoretical and empirical relationships between these parameters and changes in traditional quantitative EEG measures (Rowe et al., 2004c). Results from fitting the model to empirical EEG data indicate that states of reduced arousal, characteristic of increased delta–theta EEG, are associated with (i) larger dendritic time constants, particularly for inhibitory neurons (i.e., $GABA_B$), and (ii) increased activity in pathways involving the inhibitory TRN (Robinson et al., 2001b; 2002; Rowe et al., 2004c).

Given evidence for hypoarousal in ADHD (Satterfield & Cantwell, 1974; Satterfield & Dawson, 1971) and associated increases in delta–theta activity (Chabot & Serfontein, 1996; Clarke et al., 2001b; Lazzaro et al., 1999; Matsuura et al., 1993), it is hypothesized that ADHD subjects would show the following changes in model parameters: (i) larger dendritic time constants, and (ii) increased activity in pathways involving the TRN. In view of the signal-to-noise deficit and reduced arousal in ADHD (Pliszka et al., 1996; Volkow et al., 2001), a third hypothesis predicts (iii) an abnormal increase in the activity of cortical interneurons, predominantly inhibitory stellate types. To test these hypotheses, the biophysical model and its predictions were used to fit and replicate tonic measures of EEG data in 54 adolescent males diagnosed with ADHD and their age- and sex-matched healthy control subjects. This provided values for each physiological parameter, thereby quantifying the underlying neural activity in each individual subject and permitting subsequent comparisons between the groups.

MATERIALS AND METHODS

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; Rowe et al., 2004c). 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 modeling of experimental EEG data (Rowe et al., 2004c). For brevity the equations and numerical details have been omitted. These, including the complete methodology, are summarized in Rowe et al. (2004b), whereas the full mathematical analysis is also given elsewhere (Rennie et al., 2002; Robinson et al., 1997; 2001b). The physiological features used in the model have also been justified in previous studies (Robinson et al., 1997; 2001a; 2001b; Rowe et al., 2004c). In this study, the focus is on the ability of the model to provide physiological insight into the tonic EEG abnormalities occurring in ADHD, and whether the results are consistent with known physiology.

Neurophysiology—Mass Action—Macroscopic Approach. The neurophysiology of the model is illustrated in Figure 1. Action potentials from various neurons, represented as 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 (Figure 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., 2001b; 2004).

The mean firing rate Q_a (or *pulse density*) of the neuron (Figure 1b) is assumed to vary according to a typical nonlinear sigmoid function, such as that found in the McCulloch-Pitts neuron. The sigmoid relates the firing rate to the average membrane potential V_a, and resembles a smoothed step function (Freeman, 1975). However, if the EEG signal is treated as being due to small perturbations about a steady state, the sigmoidal response can be linearized 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

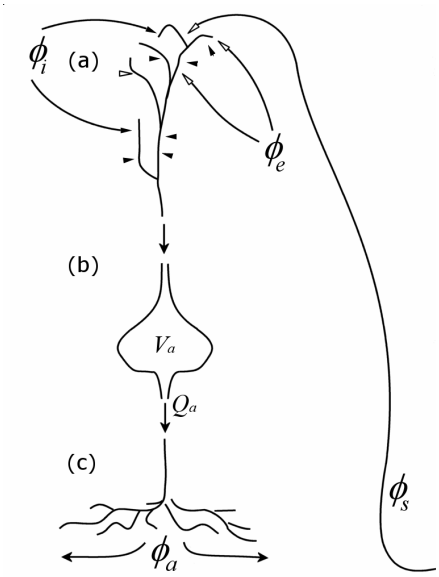

Figure 1. The basic neuronal physiology incorporated by the EEG model is illustrated in a cortical neuron showing (a) synaptic connections at the dendritic tree originating from pulse-rate fields ϕ_b ($b = i, e, s$), (b) the somatic membrane potential V_a ($a = e, i$) at the cell body with resultant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

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 fields ϕ_a (Figure 1c). The potentials propagate at an average velocity $v_a = 5$–10 m s^{-1} depending on axonal myelination (Bullier & Henry, 1979; Dinse & 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 & 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 earlier. This also uses a two-dimensional continuum, which is justified by the relative thinness of the cortex and the scale of neural modeling and experimental measures (Robinson et al., 1997; 2001b).

Cerebral Connectivity. The axonal range of intracortical inhibitory and excitatory stellate cells ($r_i \sim .1$ 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 & Schüz, 1991; Nunez, 1981). 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 (see Figure 2). Here, the

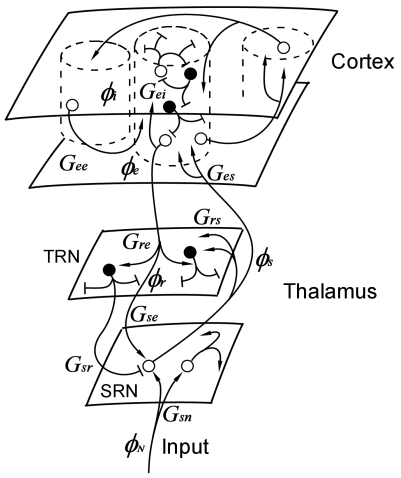

Figure 2. Schematic of pathways and connections in the model, and their anatomical significance. Open circles represent excitatory neurons and inhibitory neurons are shown with solid circles. Long-range projections are depicted by solid arrows and short-range projections by bars. (i) Local intracortical 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.

various pathways have gains G_{ab}, where additional subscripts r and n refer to the thalamic reticular nucleus (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 because 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 because the TRN consists of inhibitory GABAergic neurons. The axonal transmission through G_{ese} or G_{esre} also induces a signal delay time $t_0 \approx .085$ 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 (Robinson et al., 2001b; 2002; Rowe et al., 2004c) and are used to interpret variance in the measures in this study.

Independent Parameters. The preceding parameters with their typical parameter values are listed in column 4 of Table 1. These values were obtained from group averages of parameters generated from fits to eyes-closed spectra of 100 healthy controls during earlier experimental work (Robinson et al., 2004; Rowe et al., 2004c). 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; Rennie et al., 2002; Robinson et al., 1997; 2001b; 2004; Shwedyk et al., 1977; Stulen & 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 (Rowe et al., 2004c). 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 and 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 (Rennie et al., 2002; 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).

Table 1. Typical parameter values for the EEG and electromyogram (EMG) theoretical model spectrum as described in text

Model	Parameter	Description	Typical value
EEG model	γ_e	Cortical damping rate (υ/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

The neural gains G_{ab} reflect the input/output response characteristics of the respective neural populations, whereas other parameters reflect dendritic and axonal delays, power normalization and filtering properties of the scalp. The EMG parameter A, independent to the EEG model, is a normalization factor, which corrects for pericranial muscle artefact according to an EMG algorithm.

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

Subjects

EEG data were acquired for 54 adolescent males diagnosed with ADHD (mean age = 13.7 years; *SD* = 1.4; age range = 11–17 years) and 54 age- and sex-

matched normal control subjects (mean age = 13.4 years; *SD* = 1.5; age range = 11–17 years). All subjects were required to have had no history of neurological disorder or substance abuse. The EEGs for these subjects were obtained from a series of studies by Lazzaro et al. (1999; 2001). In these studies 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. This included 47 of the Combined type (Inattentive and Hyperactive-Impulsive) and 7 of Predominantly Hyperactive–Impulsive type.

At the time of EEG testing all ADHD subjects were unmedicated. Of the total, 34 were drug naive and 20 were withdrawn from stimulant treatment for at least 2 weeks prior to testing. Subsequently, 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). The selection criteria were based on a hyperactivity index that was 1.5 *SD*s above published norms for the Conners' Teaching Ratings and 1.0 *SD*s above the norm for the Conners' Parent Rating. The control subjects were recruited from local high schools and further evaluated to ensure no history of ADHD. Only subjects with a *T*-score of <1.0 *SD* above the norm on the Conner's Parent and Teacher Rating Scales were accepted into the studies (Lazzaro et al., 1999; 2001). The adolescents in both groups 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.

The total of 54 subjects rather than either the 47 or 7 subtype groups were used to permit comparison with the prior EEG studies examining this group. Note also that the pattern of statistical results remained very similar with the latter group removed (see Results section).

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 the midline frontal (Fz), central (Cz), and parietal (Pz) sites. During the recording subjects were awake and non-drowsy and EEGs were acquired continuously for 2 min during a resting eyes-closed condition. Ocular artifacts were corrected offline according to the method of Gratton et al. (1983). For each EEG recording the average experimental power spectrum P_{exp} from .24–49.8 Hz (204 data points) was calculated for 27 successive 4-s epochs using a fast Fourier transform analysis.

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., 2004c). To minimize noise P_{exp} was also smoothed over a full width of 1.0 Hz, as this has been found to reduce uncertainty in the model parameters (Rowe et al., 2004c). 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., 2004c).

The data fitting procedure was identical to that 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 50–210 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., 2004c). Furthermore, axonal velocity of myelinated neurons in the mammalian cortex is also expected to be within 5–10 m s^{-1} (Bullier & Henry, 1979; Dinse & Kruger, 1994), and axonal range r_e within .05–.1 m (Braitenberg & Schüz, 1991; Nunez, 1981). Therefore, given $\gamma_e = \upsilon_e/r_e$, broad limits of 50–210 s^{-1} for γ_e can be determined that approximate experimental findings (Robinson et al., 2004; Rowe et al., 2004c).

RESULTS

Quantitative EEG (qEEG) Analyses

Because the focus of this study is the physiological model parameters, for brevity the full methodological and statistical details of the qEEG analysis have been omitted, these are found in Lazzaro et al. (1999). However, a summary of these results is included to confirm the abnormal increase in

theta qEEG activity in the ADHD sample. This was determined by computing the relative and absolute qEEG power in the Delta (1.0–3.0 Hz) and Theta (4.0–7.0 Hz) bands. Each frequency band was submitted separately to a repeated two-way analysis of variance (ANOVA), with Group (control subjects vs. ADHD) as the between subject factor and Site (Fz, Cz, Pz) as the repeated within subject factor. As the central focus in this study is the between-groups effects, main effects of site were not analyzed.

Delta activity did not show any significant Group differences. However ADHD patients showed significantly increased relative ($F_{1,106} = 8.54$, $p < .005$) and absolute ($F_{1,106} = 12.6$, $p < .005$) global Theta activity. There was also a significant decrease in relative beta activity in the ADHD group compared with the control group ($F_{1,106} = 9.98$, $p < .005$). There were no significant Group × Site interactions for the midline sites for these band powers (Lazzaro et al., 1999).

Model Parameter Analyses and Data Screening

In Figure 3, one example chosen at random from each group illustrates the high accuracy of the model fits obtained for most subjects (further fit examples are available in Rowe et al., 2004c). The model is shown to match the characteristic spectral properties of the EEG closely, and with such spectra the model provided robust parameter values.

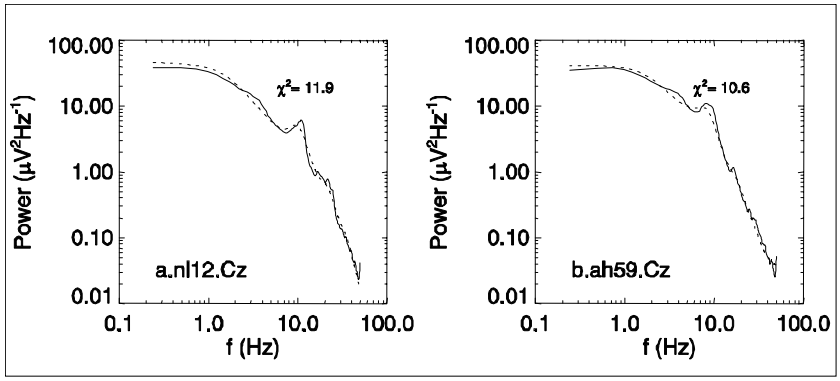

Figure 3. Sample of model fit for one subject selected at random from each group (a) ADHD and (b) healthy control. Each frame compares the subject's experimental spectrum (–) with their modelled spectrum (···), and lists the subject's ID number, site, and corresponding χ^2 value, reflecting goodness of fit.

Consistent with previous results using large sample sizes, the physiological parameter values followed a normal distribution (Rowe et al., 2004c). However, outliers did occur in limited cases where spectra did not accurately constrain and fit the complete set of physiological parameters, possibly due to noise and/or featureless spectra. It was found that 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, these outliers were accounted for by removing outlying data points (median +/– 2 SD or more) in parameters of interest, γ, α, G_{ei}, G_{ee}, G_{ese}, G_{esre}, and G_{srs}, and replacing these with the new mean. These amounted to the replacement of approximately 5% of data points within each group. Each parameter was then analyzed using the previous two-way ANOVA. Significant interactions were explored further using simple effects analysis.

Significant main effects of Group were found for the dendritic rate parameter α ($F_{1,106} = 2112$, $p < .001$, $MS_e = 295$) and intracortical gain $|G_{ei}|$ ($F_{1,106} = 4.02$, $p < .05$, $MS_e = 8.4$). These findings were consistent with hypotheses (i) and (iii) respectively, indicating longer dendritic response times and increased cortical activity (involving local stellate cells) in the ADHD group.

The final parameters worth noting were the intrathalamic gain G_{srs} and the cortical excitatory gain G_{ee}. The Group × Site interaction for G_{srs} was nearly significant at the 0.05 level ($F_{2,212} = 2.77$, $p = .06$, $MS_e = .12$), indicating $|G_{srs}|$ (involving the TRN) was greater for the ADHD group at sites Cz ($F_{1,212} = 6.09$, $p < .05$, $MS_e = 0.12$), and Pz ($F_{1,212} = 9.44$, $p < .05$, $MS_e = .12$), consistent with hypothesis (ii). The main effect for G_{ee} (involving pyramidal cells) was also nearly significant ($F_{1,106} = 3.42$, $p = .07$, $MS_e = 8.5$), showing a trend of increased activity in the ADHD group, also consistent with hypothesis (iii). No other effects were significant at the $p < .05$ level.

These trends are illustrated in Figure 4, showing that the dendritic rate parameter α is consistently lower (longer time constant) in the ADHD group across all sites. Both $|G_{srs}|$ and $|G_{ei}|$ are shown to be greater in the ADHD group, particularly at central and parietal sites.

The model parameter effects were reanalyzed using the same methodology, but with the 7 Predominantly Hyperactive–Impulsive type subjects removed. This analysis produced a similar pattern of results as found earlier with these subjects inclusive. The main effect of group for α remained significant at $p < .005$, $|G_{ei}|$ was nearly significant with $p = .05$, and for G_{ee}, $p = .09$. The Group × Site interaction for $|G_{srs}|$ was now significant at $p < .05$.

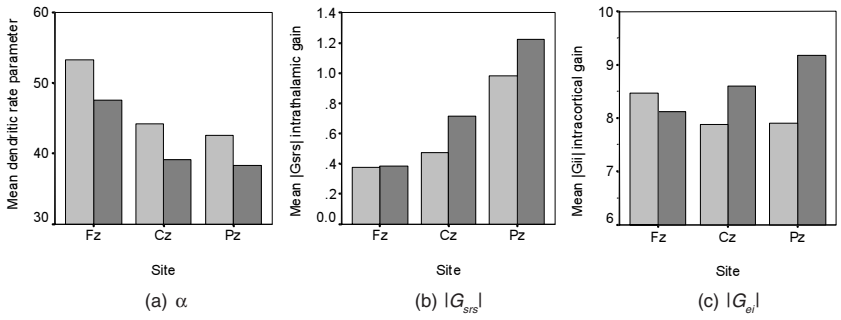

Figure 4. Mean values across site for significant parameters showing significant effects between the Control (light bar) and ADHD (dark bar) groups.

DISCUSSION

A biophysical model of brain activity has been used based on primary neural properties, cell populations, and networks, to infer physiological abnormalities underlying tonic EEG measures in ADHD. Consistent with predictions, the model has been able to significantly discriminate the ADHD subjects from their controls according to three key model parameters: (i) a decrease in the dendritic rate parameter α (longer recovery time), (ii) an increase in the magnitude of inhibitory intrathalamic gain ($|G_{srs}|$) involving the TRN, and (iii) an increase in the magnitude of intracortical (net inhibitory) gain ($|G_{ei}|$) involving local circuit inhibitory and excitatory interneurons. These differences may be interpreted with some confidence given the robustness of fits between the model and experimental data. These fits showed a very high accuracy (low χ^2) over the entire spectral range (.25–50 Hz), and the model also faithfully reproduced the inter-subject variability seen in the spectral shape (Figure 3).

The examination of ADHD subtypes requires mentioning given the important work that is being carried out in this area with respect to EEG (e.g., Clarke et al., 1998; 2001a; 2001c; Kuperman et al., 1996). However, because it is not a focus of this study, given hyperactivity was the primary selection criteria, and there was only a small number (n = 7) of the Predominantly Hyperactive–Impulsive type, the examination of ADHD subtypes with larger numbers using the EEG model is left for future work. The exclusion of the Predominantly Hyperactive–Impulsive subtype group also produced very similar statistical results with only small statistical variations, such as the Group ×

Site interaction for G_{srs} now becoming significant at $p < .05$. Therefore, the inclusion of this ADHD subgroup is not considered to alter the interpretation of results for this study, and also permits comparison with prior studies by Lazzaro et al. (1999, 2001), which included all 54 subjects. Nevertheless, the sensitivity of the model parameters is expected to increase in larger samples when examining ADHD subtypes, which are known to display heterogeneity in qEEG band powers (e.g., Clarke et al., 1998; 2001a; 2001c; Kuperman et al., 1996).

Intrathalamic Gain $|G_{srs}|$, Delta–Theta Activity and Hypoarousal

In addition to the finding of increased intrathalamic gain $|G_{srs}|$, the analysis of QEEG also confirmed that these ADHD subjects exhibited an increase in delta–theta (7 Hz) power across the midline sites compared to controls, consistent with previous results (Lazzaro et al., 1999), and other studies (Chabot & Serfontein, 1996; Clarke et al., 2001b; Matsuura et al., 1993). The present authors also found in a previous study that examined transitions in the EEG of 100 healthy subjects, that changes in relative delta and theta power were positively correlated with changes in inhibitory intrathalamic gain $|G_{srs}|$ (Rowe et al., 2004c). In this regard, the increases in intrathalamic activity $|G_{srs}|$ involving the TRN, observed for ADHD subjects in this study, may account for the known enhancements in delta–theta power in this group. This is further consistent with indications of hypoarousal in ADHD (Satterfield & Cantwell, 1974; Satterfield & Dawson, 1971) given previous experimental and theoretical studies have also shown that the TRN is involved in the generation of delta–theta (1–5 Hz) EEG rhythms during states of hypoarousal, such as drowsiness and the early stages of sleep (Destexhe & Sejnowski, 2002; Dossi et al., 1992; Robinson et al., 2001b; 2002; Steriade, 1999). However, this does not mean that ADHD individuals display spectra resembling those seen in sleep (Figure 3), but that some spectral components, found particularly in sleep, appear abnormally enhanced.

Intracortical Gain $|G_{ei}|$ and Hypoarousal

The finding of increased intracortical gain $|G_{ei}|$ in the ADHD group can also support the hypoarousal theory. Recent work in a previous article has shown

that this parameter is both theoretically and experimentally associated with changes in the slow wave (<1 Hz) component of the EEG (Rowe et al., 2004c). This frequency range is not typically cited in EEG studies; however, increases in $|G_{ei}|$ alone tend to lead to a flattening of this spectral component as an indicator of over-stability. This characteristic is also found during reduced arousal and the early stages of sleep (Robinson et al., 2001b). Generally the firing activity of these inhibitory neurons $|G_{ei}|$ closely follows the activity of their excitatory counterparts G_{ee} to maintain stability in the cortex, and prevent runaway inhibitory and/or excitatory activity (Rowe et al., 2004b). An abnormal tonic increase in one of these populations in ADHD would be expected to have significant debilitating effects on the efficiency of information processing in the cortex.

Dendritic Rate Parameter α and GABA Responses

The increase in $|G_{ei}|$, predominantly GABAergic neuronal types, is consistent with the finding of a lower dendritic rate parameter α (slower response) in the ADHD group, because time constants for GABAergic neurons are longer than those of glutamatergic pyramidal (predominantly AMPA) neurons (Thomson et al., 1996; Thomson, 1997). Reductions in α also reflect an attenuation of high frequency (>20 Hz) EEG signals (Robinson et al., 2001b; Rowe et al., 2004c), which would be likely to interfere with the efficiency of cognitive and sensorimotor processes known to occur within the high-frequency bands [e.g., gamma EEG (Haig et al., 2000)]. The attenuation of high-frequency EEG in these subjects is consistent with the findings by Lazzaro et al. (1999) who found a reduction in relative beta (130 Hz) levels in this subject group and in other studies (Callaway et al., 1983; Mann et al., 1992).

These findings are particularly relevant to the hypoarousal theory because activation of GABA receptors are preferentially associated with reduced arousal and sleep, particularly in the subcortex and inhibitory interneurons (TRN) of the thalamus (Contreras et al., 1996; Juhasz et al., 1994; Kim et al., 1997). Furthermore, the sedative and anxiolytic effects of benzodiazepines and barbiturates, and anesthetics such as halothane and isoflurane are known (at least in part) to produce their effects through marked potentiation of GABA responses (Farrant, 2001). These examples of reduced states of arousal are also characterized by enhanced slow wave, delta, and theta activity, but reduced high-frequency (>8 Hz) activity (Niedermeyer & Lopes da Silva, 1999). Such effects occurring in ADHD would be expected to significantly impede the efficiency of information processing and attention.

Interneurons and Information Processing

The increase in $|G_{ei}|$ may also directly relate to the primary breakdown in the mechanisms of selective attention and signal processing proposed in ADHD (Pliszka et al., 1996; Volkow et al., 2001). This is possible because the activation of these neuronal types in the neocortex, particularly the fast-spiking GABAergic interneurons, is not necessarily solely an indication of reduced arousal, but may also reflect an increase in cortical noise and interference. Given neural gains $G_{ab} = \rho_a N_{ab} s_b$ are proportional to firing rate, and the number N_{ab} and response strength s_b of synapses, the increase in $|G_{ei}|$ suggests an overall increase in the tonic firing rate and/or the synaptic activity of local excitatory and inhibitory interneurons during minimal sensory processing and cognitive demand (eyes-closed). This is opposite to previous findings where increases in cortical gains were associated with an increase in sensory processing (e.g., eyes-open), rather than minimal sensory processing, although this was for both $|G_{ei}|$ and G_{ee} (Rowe et al., 2004b). A tentative interpretation of these results is expanded on in the following sections and is summarized as follows: (i) The brains of the ADHD individuals may excessively process extrinsic information during periods of minimal sensory load, consistent with the role of interneurons in the rapid control of neural activity in intracortical networks (Beierlein et al., 2002; Gupta et al., 2000). (ii) Their brains may simply be noisier as neurons continue to "chatter" during minimal sensory processing and cognitive demand, suggesting they lack functional mechanisms to suppress this intrinsic cortical activity. (iii) Or it may relate to the hypoarousal theory as discussed earlier, assuming an increase in the action of inhibitory interneurons (like the TRN) can also indicate reduced cortical arousal.

Neurochemical Mechanisms

The EEG model is based on a quantification of the average properties of certain neural sub-populations, and inverse modeling allows values to be inferred for the parameters that characterize these sub-populations. These values, such as the gains G_{ab}, are combinations of factors (e.g., synaptic distributions on dendrites, cell subtypes, resting potentials, extracellular conditions) that are more fundamental. At this stage quantitative models of large-scale EEG do not explicitly incorporate all available neurophysiological details, although the most relevant are being incorporated in current and future work. For now the bridge between quantifications and the ultimate mechanisms

remains somewhat speculative, but provides groundwork for future studies. It is with this context in mind that the following sections consider potential interpretation and neurochemical mechanisms that may account for the abnormal variation found in the neural gains in ADHD studies.

Acetylcholine

Recent evidence suggests that individuals with ADHD may have abnormalities in the cholinergic system (Biederman & Spencer, 2000; Spencer et al., 2000). This system uses acetylcholine (ACh) and other ligands to modulate various excitatory (e.g., AMPA, NMDA) and inhibitory (e.g., GABA) processes throughout the cortex (Sarter & Bruno, 2000). Nicotine, which activates cholinergic nicotinic ACh receptors (nAChRs), has been found to improve symptoms in individuals with ADHD (Conners et al., 1996; Levin, 2002; Wilens et al., 1999), 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).

The finding of increased intracortical $|G_{ei}|$ and intrathalamic $|G_{srs}|$ gains in ADHD can be accounted for by a reduction in the tonic activity of the cholinergic system. In addition to exerting tonic affects on cortical arousal, the cholinergic system can suppress the intrinsic activity of cortical circuits while enhancing TC inputs and receptivity to external stimuli (Hasselmo, 1995; Oldford & Castro-Alamancos, 2003). Cholinergic activity leads to inhibitory and excitatory effects. The activation of metabotropic muscarinic ACh receptors (mAChRs) strongly suppresses the activities of intracortical interneurons, whereas the activation of ionotropic nAChRs on TC terminals increases glutamatergic responses, thereby enhancing TC input (Gil et al., 1997; Kimura & Baughman, 1997; Koós & Tepper, 2002). The muscarinic mechanisms generate a tonic (slow, but sustained) reduction in the intrinsic noise or "chatter" generated by the dominating neocortical cells (Douglas et al., 1995; Gil et al., 1999; Zador, 1999), so that external inputs from the fewer, but modality-specific, TC inputs can be processed successfully in associated networks, assisted by the rapid nAChRs mechanisms. Therefore, increases in tonic intracortical activity $|G_{ei}|$ in ADHD in the absence of active sensory processing may reflect a deficit in this mechanism of muscarinic suppression, such that spurious signals, or ones that are meant to be inhibited, are not. This view is broadly consistent with the proposed executive

function deficits (Barkley, 1997) and deficits in the frontal lobe inhibitory system (Barry et al., 2003).

The finding of increased intrathalamic gain $|G_{srs}|$ in ADHD can also be explained by an abnormal reduction in cholinergic activity and therefore hypoarousal. During waking states and REM sleep the activity of the cholinergic system increases, whereas during drowsiness and the early stages of sleep there is a decrease (Jasper & Tessier, 1971; Jones, 1993; Vazquez & Baghdoyan, 2001). Increased cholinergic activity enhances the depolarization of TC cells via nAChR activation (Curro et al., 1991; McCormick, 1990), but tonically suppresses the activity of the TRN via the activation of M2 mAChRs, also indirectly enhancing TC activity (Cox & Sherman, 2000; McCormick & Prince, 1986; Steriade, 1999). In contrast, reductions in cholinergic activity lead to increased activity in the TRN (i.e., increased $|G_{srs}|$) due to disinhibition. In turn, increased TRN activity leads to the inhibition (hyperpolarization) of TC cells (Losier & Semba, 1993; Steriade et al., 1986; Timofeev et al., 1996). This can lead to a reduction in alpha and beta activity via reduced G_{ese} (Robinson et al., 2001b; Rowe et al., 2004b), consistent with findings showing reduced beta activity in ADHD (Clarke et al., 2001b; Lazzaro et al., 1999), an indirect consequence of hypoarousal in this context. Therefore, deficits in tonic levels of ACh can lead to disinhibition of the TRN and increased $|G_{srs}|$, suggesting that individuals with ADHD may also be suffering from overactivity of the TRN, leading to hypoarousal. This is consistent with the hypoarousal model (Satterfield & Cantwell, 1974) and findings of reduced skin conductance response (Lazzaro et al., 1999), indicating low cortical arousal (Satterfield & Dawson, 1971), elevated delta–theta, and reduced beta EEG activity (Barry et al., 2003; Defrance et al., 1996) in ADHD subjects.

Norepinephrine and Dopamine

Of further importance are medicinal effects of methylphenidate and dextroamphetamine on ADHD symptoms (Anastopoulos et al., 1991; Swanson & Volkow, 2002; Zeiner et al., 1999), drugs that increase cortical NE levels and act via the NA and DA systems (Pliszka et al., 1996; Solanto, 1998). Like the cholinergic system, the activity of NA system is associated with states of increased arousal and wakefulness promoting actions (Berridge & Waterhouse, 2003). During aroused states, the firing of NA, LC, and DA neurons increases (Gottesmann, 2002a; Trulson & Jacobs, 1979) and this is thought to improve signal-to-noise ratio in the cortex by using similar metabotropic receptor mechanisms to the cholinergic system (Curet et al., 1992; Hasselmo

et al., 1997; Segal & Bloom, 1976; Volkow et al., 2001). Stimulation of the LC, in addition to the application of NE, also leads to increased depolarization of both the TRN and TC relay cells (McCormick, 1989). In contrast, stimulant medications decrease the baseline tonic firing of the LC via the activation of metabotropic α-2 receptors (Curet et al., 1992; Graham & Aghajanian, 1971; Ramirez & Wang, 1986), similar to the effects of Clonodine (Pliszka et al., 1996). These results suggest that stimulant medications may act to decrease the activity of the TRN by suppressing LC afferents to the TRN, given this effect outweighs the direct extracellular effects of NE administration on increasing TRN depolarization (Rowe et al., 2004). Thus, supporting the hypothesis that individuals with ADHD may suffer from overactivity of the LC (Konrad et al., 2003; Pliszka et al., 1996; Solanto, 1998) in addition to reduced activity of the cholinergic system and overactivity of the TRN leading to hypoarousal.

Neurotransmitter Interactions between Acetylcholine, Norepinephrine, and Dopamine

Many of the effects of the NA system on arousal and attention may also occur through interaction with the cholinergic system (Koyama & Kayama, 1993; Zaborszky et al., 1993). This may occur via NA projections from the LC to the forebrain, brainstem, and cortical areas rich in cholinergic neurons (Aston-Jones et al., 1999; Dringenberg & Vanderwolf, 1998), which appear to enhance cholinergic activity (Fort et al., 1995; Tellez et al., 1999). These results suggest stimulant drugs might increase cholinergic activity by increasing the levels of extracellular NE, assuming that this outweighs the reduction in LC activity. Similarly, the influence of dopamine on arousal and/or cortical activation may also occur indirectly via DA excitation of basal forebrain cholinergic cells (Dringenberg & Vanderwolf, 1998; Jones & Cuello, 1989; Smiley et al., 1999), thereby increasing the release of ACh in the cortex (Casamenti et al., 1986; Levin, 2002; Pepeu & Bartolini, 1968). Alternatively, DA activity may (in turn) be increased by cholinergic and glutamatergic neurons from the mesopontine tegmental area (Grenhoff et al., 1986; Lavoie & Parent, 1994; Miller et al., 2002).

With these results in mind, the proposed "over-activity" of the LC in ADHD (Pliszka et al., 1996; Solanto, 1998) may seem inconsistent with the proposed "reduced activity" of the cholinergic system. Over-activity of the LC may be expected to lead to an increase in the activity of the cholinergic system, rather than a decrease, because LC activity can lead to stimulation of

the cholinergic system. Similarly, an increase in LC activity may also be expected to enhance signal-to-noise ratio via metabotropic receptor activation. However, differences in expected results and effects can be accounted for by the various subtype NA receptors, which differ in neuromodulatory effects and desensitization rates (Hasselmo et al., 1997; Summers et al., 1997; Suzuki et al., 1990).

Theta and Alpha Peaks

Of particular interest are the subjects who show both theta and alpha peaks. The model does not appear to capture the theta peaks in some subjects completely, suggesting some of the effects in the neurophysiological parameters may be underestimated. In particular, a greater proportion of "negative" feedback (rather than positive) via the corticothalamic-TC pathway G_{esre} involving the TRN has also been shown to lead to an enhancement in the delta–theta resonance, but also proportionate decreases in the alpha and beta resonance, particularly for reduced arousal (Robinson et al., 2001b; 2002; Rowe et al., 2004b), as found in some ADHD subjects (Clarke et al., 2001b; Lazzaro et al., 1999). The TC projection system shows strong modality specificity and topographical specialization (Montero, 2000; Newman, 1995). Therefore, there may be separate TC-corticothalamic pathways with functional specificity that are influencing the alpha resonance, whereas others involving the TRN are influencing the delta–theta resonance.

The EEG model does have the capacity to model both alpha and delta–theta peaks (Robinson et al., 2001b), however there is difficulty in generating both peaks simultaneously. These two spectral features generally reflect incongruous states (wake versus sleep) that are not often simultaneously present in the healthy brain, at least for tonic measures of neural activity. This phenomenon may be simulated by more complicated network structures where some networks are subject to excess negative feedback via the inhibitory TRN, whereas others receive more positive feedback via the excitatory TC relay neurons. Such variant TC activity across the cortex may also become more apparent with full topographical modeling. Alternatively the delta–theta rhythm may arise due to increased activity in cortico-hippocampal feedback loops (Kahana et al., 1999). However, given the hypothesis of tonic hypoarousal in preference to hippocampal memory-related abnormalities (presumably phasic), the possibility of tonic abnormalities in TC mechanisms involving the TRN seems more likely. Alternatively, it is possible that theta and alpha peaks are being generated independently during separate epochs. This

suggests that in future work, smaller averages, or careful selection of epochs may be required to examine these data thoroughly, but this would be at the expense of signal-to-noise.

CONCLUSION

The aforementioned results suggest that the potential neurochemical mechanisms underlying ADHD may be more complicated than previously thought, and it is not possible to attribute ADHD to the failure of a single neurotransmitter system, but to a complex set of imbalances occurring in different neurotransmitters and neural networks. Here this has been considered as an "overactivity" in a number of systems including inhibitory interneurons (G_{ei}) in the neocortex and the TRN that seem particularly consistent with larger dendritic time constants (α) and a state of over-inhibition, leading to reduced arousal. The increase in $|G_{ei}|$ relating to the slow wave component of the EEG spectra can be further accounted for by reduced activity of cholinergic and/or NA metabotropic receptor activation which normally acts to suppress intrinsic cortical noise and neural "chatter." In contrast, enhancements in delta–theta EEG activity can be accounted for by an increase in intrathalamic gain (G_{srs}) involving the inhibitory TRN, and therefore reduced arousal. This can occur due to disinhibition of the TRN from reduced activation of cholinergic M2 mAChRs and/or increased stimulation of the TRN from LC overactivity. Therefore, in addition to the abnormal activity of neocortical interneurons and their interference in the processing of specific TC inputs, a state of suboptimal arousal may also interfere with signal processing and attention.

It is also noted that the electrophysiological responses examined in this article are that of "tonic" baseline activity in the EEG rather than the "phasic" EEG activity apparent in the examination of event-related potentials (ERPs). The latter incorporate more complex temporal cortical dynamics, as discussed in Rennie et al. (2002). However, the current study of tonic cortical mechanisms has allowed the determination of some of the potential tonic abnormalities that may be occurring in ADHD. In future work the authors aim to apply the same principles and similar methodology to EEG measures from multiple scalp sites in addition to midline, and varying cognitive states and ERPs in ADHD, including their subtypes. The neurochemical hypotheses proposed in this study relating to NA and cholinergic mechanisms can also be tested in future studies aimed at determining the physiological action of drugs in ADHD, particularly relating to affects on primary neural populations and circuitry (Rowe et al., 2004a).

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