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The quantified EEG characteristics of responders and non-responders to long-term treatment with atomoxetine in children with attention deficit hyperactivity disorders

Giuseppe Augusto Chiarenza [a,b,*,1], Robert Chabot [c], Robert Isenhart [c], Luciano Montaldi [a,b], Marco Paolo Chiarenza [b], Maria Grazia Lo Torto [a,b], Leslie S. Prichep [c]

[a] Child and Adolescent Neuropsychiatry Dept., Rho Hospital, Milan, Italy
[b] International Center Learning, Attention and Hyperactivity Disorders (CIDAAI), Milan, Italy
[c] Brain Research Laboratories, Dept. Psychiatry, New York University, NY, United States

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ABSTRACT

Objective: The aim of our study is to examine quantitative Electroencephalogram (QEEG) differences between ADHD patients that are responders and non-responders to long-term treatment with Atomoxetine at baseline and after 6 and 12 months of treatment. Patients with attention deficit hyperactivity disorder (ADHD) received atomoxetine titrated, over 7 days, from 0.5 to 1.2 mg/kg/day. QEEG and Swanson, Nolan, and Pelham–IV Questionnaire (SNAP-IV) scores were recorded before treatment and after therapy.

Methods: Twenty minutes of eyes closed resting EEG was recorded from 19 electrodes referenced to linked ear-lobes. Full frequency and narrow band spectra of two minutes of artifact-free EEG were computed as well as source localization using Variable Resolution Electrical Tomography (VARETA). Abnormalities were identified using Z-spectra relative to normative values.

Results: Patients were classified as responders, non-responders and partial responders based upon the SNAP-IV findings. At baseline, the responders showed increased absolute power in alpha and delta in frontal and temporal regions, whereas, non-responders showed increased absolute power in all frequency bands that was widely distributed. With treatment responders' absolute power values moved toward normal values, whereas, non-responders remained at baseline values.

Conclusions: Patients with increased power in the alpha band with no evidence of alterations in the beta or theta range, might be responders to treatment with atomoxetine. Increased power in the beta band coupled with increased alpha seems to be related to non-responders and one should consider atomoxetine withdrawal, especially if there is persistence of increased alpha and beta accompanied by an increase of theta.

1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is the most common neurobehavioral disorder of childhood. The essential feature of ADHD is a persistent pattern of inattention and/or hyperactivity that interferes with functioning or development and causes impairment in multiple settings: home, school and work. Population surveys suggest that in most cultures ADHD occurs in about 5% of children (Szatmari, 1992.) In general ADHD is more frequent in males than females, with an approximate 2:1 ratio in children. Its course is chronic in 30–50% of the affected children (American Psychiatry Association, DSM-V, 2013).

Extensive neuroimaging studies (QEEG, VARETA, ERPs, PET, fMRI) have demonstrated that during the execution of cognitive tasks, children with ADHD show a pattern of hypoactivation of the prefrontal lobes and of the striatal regions (di Michele et al., 2005; Lou et al., 1984, 1989; Rubia et al., 1999, 2001, 2011; Hastings and Barkley, 1978; Klorman, 1992; Taylor, 1986). Neuropsychological studies have also shown the impairment of several executive functions (sustained, focused and divided attention, working memory, response inhibition, time perception, flexibility, programming and delayed reward response). These executive functions are located in the frontal and prefrontal lobes and in particular in the dorso-lateral prefrontal cortex (Barkley, 1977a, 1997b; Barkley et al., 1992; Goodyear and Hynd, 1992). Neuropharmacological studies both in humans and animals have demonstrated that these executive functions are mediated by noradrenergic and dopaminergic neurotransmitters, adding more evidence of a probable deficit of these circuits in ADHD (Arnsten and Li, 2005; Hunt et al., 1988; Rapaport and Zametkin, 1988; Shaywitz

* Corresponding author at: CIDAAI, Centro Internazionale dei Disturbi di Apprendimento, Attenzione e Iperattività, via Edolo 46, 20163 Milano, Italy.
E-mail address: giuseppe.chiarenza@fastwebnet.it (G.A. Chiarenza).

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and Shaywitz, 1984; Shaywitz et al., 1983; Zametkin and Rapoport, 1986). Furthermore, Castellanos et al. (1994, 1996) have shown that in ADHD adults there is an evident reduction of the volume of some cerebral areas, including the right prefrontal areas, the nucleus caudatus, the globus pallidus and the cerebellum. It has been suggested that ADHD children show a maturational lag in the development of these cortical regions and their interconnections (Barry et al., 2003, 2009b). This maturational lag has been associated with elevated slow wave activity and deficiencies of fast wave. Elevated high amplitude theta with deficiencies of beta activity was associated with hypoarousal and excess beta activity was tentatively interpreted as hyperarousal. This profile has been found primarily in children with the combined type of ADHD (Chabot et al., 1999; Clarke et al., 2001d). All these studies used very restrictive ADHD inclusion criteria, with children with comorbidities being excluded (Clarke et al., 1998, 2001a, 2001c, 2001d). However, in line with recent works that links arousal abnormalities with global alpha activity (Barry et al., 2009b), the hyperarousal hypothesis as the underlying CNS abnormality was not confirmed (Clarke et al., 2011). On the other hand, Jaworska et al. (2013) examining QEEG relationships between anger and non-angry adults with ADHD noted increased beta 1 associated with anger and it was interpreted as modest resting cortical hyperarousal.

Recent evidence indicates that quantitative Electroencephalogram (QEEG) is a powerful tool in pharmaco-EEG applications. The identification of treatment responsive QEEG subtypes have been described in depression (Leuchter et al., 2009a, 2009b), obsessive compulsive disorder (Prichep et al., 1993; Hansen et al., 2003) and schizophrenia (John et al., 2007), suggesting that understanding of the underlying neurophysiology of the patient can contribute significantly to treatment optimization. QEEG has been shown to distinguish between ADHD responders (R) and non-responders (NR) to stimulant medication with sensitivity levels that fell between 68.7% and 81% with response to stimulants related to ADHD subtypes based upon QEEG profile differences (di Michele et al., 2005; Ogrim et al., 2014). Barry et al. (2007, 2009a) investigated the effects of a single dose of a selective inhibitor of norepinephrine transporters (SNRI), atomoxetine (ATX), on the electroencephalogram (EEG) and performance of children with ADHD. After 1 h ATX produced significant global increases in absolute and relative beta, with several topographic changes in other bands. This was accompanied by a significant reduction in omission errors on a Continuous Performance Task. The authors concluded that SNRIs can produce substantial normalization of the ADHD QEEG profile, together with behavioural performance improvements.

It has been previously shown that atomoxetine increased extracellular concentrations of norepinephrine (NE) and dopamine (DA) in prefrontal cortex (Viggiano et al., 2004). Furthermore, chronic administration of atomoxetine for 21 days also increased NA and DA, but not 5-HT, levels in the prefrontal cortex. Acute and chronic atomoxetine increased the expression of c-Fos, a neuronal activity marker in the prefrontal cortex, but not in the striatum. These results suggest that acute and chronic administration of ATX selectively activate the prefrontal catecholamine systems in mice (Koda et al., 2010).

At the moment, in Italy, the drugs available and currently being used for the pharmacotherapy of ADHD are: methylphenidate (MPH) and atomoxetine. We are not aware of studies that measured the effect on the QEEG of long-term treatment of ATX in children with ADHD. In the light of personalized medicine and in order to reduce this gap, the aim of this study is to examine whether QEEG subtypes are related to treatment response to Atomoxetine in ADHD. We hypothesize: 1. at baseline both R and NR will have QEEG absolute power findings consistent with those reported in the literature to include increased power in delta, theta or alpha especially in frontal and anterior temporal regions (Chabot et al., 2001; Barry et al., 2003, 2009b); 2. absolute power increases at baseline will be greater in NR than in R especially in the delta and theta frequency bands; 3. increased absolute power findings in R will decrease as a function of treatment with atomoxetine, whereas, increased absolute power in NR will not change as a function of treatment with atomoxetine; 4. QEEG source localization using VARETA will reveal more widespread abnormal findings in NR than R when compared to the normal population of children; and 5. after 12 months of treatment with atomoxetine the R will show decreased abnormal activity, whereas, NR will remain at baseline levels.

2. Material and methods

This study was conducted by recruiting consecutive patients from the ADHD Centre of the Child and Adolescent Neuropsychiatry Department of Rho hospital. The following protocol was approved by the Ethical Committee of the hospital.

2.1. Clinical protocol

2.1.1. Inclusion criteria

Patients between 6 and 16 years of age were included in the study if they met all of the following criteria: patients met DSM-IV diagnostic criteria for ADHD (any subtype), scored at least 1.5 standard deviations above the age norm for their diagnostic subtype using published norms for the Swanson, Nolan, and Pelham–IV Questionnaire (SNAP-IV) (Swanson, 1992) subscale scores, and scored above one of the given cut-offs (T-score > 55) of the Conners subscale based on age and gender (Conners, 1997). Laboratory results, including serum chemistries, hematology, and urine analysis, showed no clinically significant abnormalities. An ECG was performed to exclude cardiac diseases at the baseline/screening visit.

2.1.2. Exclusion criteria

Patients were excluded from the study if they met any of the following criteria: presence of documented psychiatric disorders of the parents, weight <20 kg at baseline visit, a documented history of Bipolar type I or II disorder, history of psychosis or pervasive developmental disorder, seizure disorder, head injury with loss of consciousness or concussion, migraine, neurological/systemic medical disease (e.g.: lupus, diabetes) or with history of stroke or arterious-venus malformation or brain surgery. Comorbid non-psychotic psychiatric disorders (not more than two) were not an exclusion criteria but were documented. Functional comorbidities such as visual or auditory processing problems were not an exclusion criteria, but were documented with above IQ testing. Additional exclusion criteria were: serious suicidal risk as assessed by the investigator, history of alcohol or drug abuse within the past 3 months or currently using alcohol or drugs, current or past history of hypertension, narrow angle (Angle-Closure) glaucoma, uncontrolled hyperthyroidism or hypothyroidism, use of monoamine oxidase inhibitors, pregnant, breastfeeding young women and sexually active who do not use a medically acceptable method of contraception.

2.2. Phase 1 protocol

The study consisted of two phases. During phase 1 the screening and assessment were conducted according to the following protocol. Family history was obtained by clinical interviewing one or both parents. The patients were diagnosed as children or adolescents with ADHD according to the DSM-IV. At the first visit, after explaining to the patient and the parent/caretaker the purpose and the procedures of the study, informed consent was obtained from both parents, adolescents and children. Adequate time to consider the information was provided. In the assessment phase the following information was obtained: demographics, medical and psychiatric history, previous and concomitant medications, physical and neurological examination, laboratory samples, Electrocardiogram (ECG), QEEG, Amsterdam Neuropsychological Test (ANT, de Sonneville, 2014) a battery to test executive functions