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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

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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

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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

and attention, SNAP-IV ADHD scale revised (SNAP IV - Swanson, 1992; Gaub and Carlson, 1997), Conners' rating scale-R for teachers (CTRS-S - Conners, 1997), Clinical Global Impressions–ADHD-Severity (CGI-ADHD-S, Guy, 1976). Children Depression Rating Scale, derived from the Hamilton Rating Scale for Depression (HAM-D), Paediatric Anxiety Rating Scale (PARS) were used to exclude mood and anxiety disorders. All patients were free of any medications according to the following guidelines for medications washouts: patients who were taking any medication that had a half-life >24 h had a washout equal to a minimum of 5 half-lives of the parent compound and any active metabolite of the parent compound prior to the second visit; patients who were taking any health food supplements that in the investigator's opinion had a central nervous system activity (for example, melatonin) had a washout equal to a minimum of 5 half-lives of that supplement prior to the second visit. If the half-life of the supplement was unknown, then the patients had a 28-day washout; no patient used monoamine oxidase inhibitors (MAOIs) during the 2 weeks (14 days) prior the first visit.

2.3. Phase 2 protocol

The second phase consisted of follow-up visits after the beginning of atomoxetine therapy, conducted at 3, 6 and 12 months. The tests administered in every subsequent visit were the SNAP-VI ADHD scale, CTRS-S, CGI, ANT and QEEG. We report only the QEEG and the SNAP results for brevity.

2.4. Atomoxetine treatment

The atomoxetine drug was titrated, in 7 days, from 0.5 mg/kg/day (dose ranging from 0.5 to 0.8 mg/kg/day) to the target dose of 1.2 mg/kg/day (range from 0.8 to 1.2 mg/kg/day). The total daily dose was administered once daily in the morning. If patients while taking atomoxetine at the target dose developed intolerable side effects, but were gaining a therapeutic benefit regarding their ADHD symptoms, the investigator administered atomoxetine in 2 divided doses (in the morning and in the evening). The dosing regimen was chosen on the basis of the research literature (Weiss et al., 2005; Kelsey et al., 2004; Michelson et al., 2002).

Safety assessment was monitored throughout the study by a qualified physician who reviewed every patient's safety data with the patient and/or parent at each visit. Adverse events were collected by open-ended discussion at all visits. Subject compliance was assessed at each visit by direct questioning. Patients were asked to return both used (including empty) and unused bottles distributed on the previous visit. No concomitant medications were present during ATX treatment.

2.5. Neurophysiologic assessment

2.5.1. EEG data acquisition

Twenty minutes of eyes closed resting EEG were recorded from 19 electrodes, using Electro-caps which place the sensors in accordance with the International 10/20 Electrode Placement System, referenced to linked earlobes. A differential eye channel (diagonally placed above and below the eye orbit) was used for the detection of eye movement. All electrode impedances were below 5000 Ω. The EEG amplifiers had a bandpass from 0.5 to 70 Hz (3 dB points). All EEG data was collected on the same digital system compatible with the demands of the protocol in order to achieve amplifier equivalence. A standard calibration system was provided with the digital EEG machine. Data were sampled at a rate of 256 Hz with 12 bit resolution. In order to avoid drowsiness during EEG recordings and to have similar conditions throughout the different sessions, all the patients were recorded in the morning, instructed to keep their eyes closed and stay awake. Patients were monitored with a closed circuit television system, throughout EEG recording. EEG was recorded before therapy (baseline) and after 3, 6 and 12 months of therapy.

2.6. EEG data analysis

The raw EEG data were visually edited by trained EEG technologists, to identify and eliminate biological (e.g., muscle movement, EMG) and non-biological (e.g., electrical noise in the room) artifacts. This was augmented by a computerized artifact detection algorithm. Two minutes artifact-free data, collected from the beginning of the EEG recording were then submitted to frequency analysis (FFT) and features log transformed to obtain Gaussianity (John et al., 1980; Gasser et al., 1982). Absolute power values for each electrode position and for the delta (1.2–3.5 Hz), theta (3.5–7.5 Hz), alpha (7.5–12.5 Hz) and beta (12.5–25.0 Hz), frequency bands are reported in this paper. All absolute power values were Z-transformed relative to the difference between normative values and the values obtained from each individual child (John et al., 1983, 1988). Significant test re-test reliability for these measures has been demonstrated (John et al., 1983; Kondacs and Szabo, 1999).

2.7. QEEG source analysis

Two minutes of artifact-free EEG was also submitted for computation of source localization using Variable Resolution Electrical Tomography (VARETA) (Bosch-Bayard et al., 2001). With this method, very narrow band (VNB) spectra were computed using FFT with bins 0.39 Hz wide from 1.5–20 Hz, for every electrode derivation. Abnormalities in these data were identified using Z-spectra computed relative to normative values. The scalp electrode positions were placed in spatial distribution with a probabilistic MRI Brain Atlas (Evans et al., 1994). The mathematically most probable underlying sources of QEEG abnormalities recorded on the scalp were then superimposed upon MRI slices from that Atlas, and the values computed for each frequency in every voxel were encoded using a color palette with hues proportional to the standard- or Z-scores of deviations from expected normative values. The significance levels of the images take into consideration the large number of measurements made, using the correction introduced by Worsley et al. (1995). The anatomical accuracy of the functional QEEG source localization obtained by VARETA and other QEEG-based source localization methods has been repeatedly confirmed by co-registration with other brain imaging modalities e.g. functional magnetic resonance, fMRI (Mulert et al., 2004), positron emission tomography, PET (Zumsteg et al., 2005; Bolwig et al., 2007), and computerized tomography (Prichep et al., 2001).

2.8. Subjects

After screening and assessment, 61 children and adolescents, 52 male (85.25%) and 9 female (14.75%), 7–16 years of age (mean age 10.36 s.d. 2.85) with ADHD with or without co-morbidities, who meet DSM-IV criteria for ADHD, agreed to participate in the experiment. 41 (69.49%) belonged to ADHD combined type, 16 (27.12%) to the inattentive type and 2 (3.39%) to the hyperactive-impulsive type. The subjects were of normal intelligence with a total IQ of 101.09 s.d. 14.29, verbal IQ 101.27 s.d. 15.66, and performance IQ 99.17 s.d. 13.5 (WISC-III). Table 1 reports the presence of comorbidities of the total sample.

A total of 37 patients (60.6%), mean age 10.29 (s.d. 2.30) continued therapy for 6 and 12 months (33 M and 4 F). Of these 37 patients, 27 subjects belonged to ADHD_Combined type, 9 subjects to ADHD_inattentive type and 1 subject to ADHD_hyperactive type. 24 subjects (39.4%) discontinued ATX: 8 for side effects (tachyarrhythmia, increased blood pressure, syncope, allergic reaction, increased irritability) of which 2 were switched to MPH; 7 dropped out for low compliance of parents.; 8 for absence of positive outcome (2 subjects were switched to MPH); and 1 for “early” positive outcome.

Table 1
Reports the presence of comorbidities and percentage in the total sample of children with ADHD.

Comorbidity	Patients	%
Oppositional Defiant Disorder	23	37.70%
Specific learning disorder	15	24.59%
Anxiety disorder	4	6.56%
Conduct disorder	2	3.28%
Language disorder	2	3.28%
Generalized learning disorder	1	1.64%
Conduct disorder + anxiety disorder	1	1.64%
Language disorder + anxiety disorder	1	1.64%
Tics	1	1.64%
None	11	18.03%
Total	61	100.00%

2.9. Statistical analysis

Preliminary statistical analyses were conducted on those 37 patients for whom data was available 6 months after the initiation of therapy. These subjects were classified as responders (R), non-responders (NR) or partial responders (PR) based upon an increase/decrease of SNAP Z scores values between baseline and each of the time points (treatment). Subjects with a 30% increase or greater in SNAP scores were classified as responders. Subjects with a decrease of 30% or more in SNAP scores were called Non-Responders. All others were classified as partial responders. Age, SNAP-Inattentive, SNAP-Hyperactivity, SNAP-Combined and SNAP-Oppositional scores for R, NR, and PR patients at baseline, 3, 6 and 12 months were submitted to two way analysis of variance (ANOVA) with levels corresponding to response type (R, NR, and PR) and time (baseline, 3, 6, 12 months). In order to reduce the number of statistical comparisons and to simplify the QEEG findings all reported analyses included only the R and NR patient groups. The only QEEG variables used to compare responders and non-responders were Z-score absolute power from 19 monopolar regions for the delta, theta, alpha, and beta frequency bands. Separate ANOVAs were conducted for the differences between responders and non-responders for each electrode location and each frequency band. The $p < 0.005$ criteria were used to determine statistical significance in order to account for the use of multiple ANOVAs (19 electrodes by 4 frequency bands). The QEEG results are displayed as a set of maps color coded by the F values corresponding to the differences between the 2 groups.

The same type of analysis was conducted within each group only for R and NR, between BL and 3 months between BL and 6 months, BL and 12 months, separately. The results are displayed as a set of maps color coded by the F value of the significance of the differences between the 2 groups.

3. Results

3.1. Atomoxetine

Atomoxetine had a positive effect on 21 subjects (55.6%), of which 11 (27.8%) were classified as responders and 10 (27.8%) as partial responders. 16 subjects, (44.4%) were defined as non-responders according to the criteria defined above. Table 2 shows the distribution of the comorbidities of children with ADHD divided in R, PR and NR. As seen in the group of NR there is a higher rate of Oppositional Defiant Disorder (ODD) compared to the other 2 groups. The other more frequent comorbidity, specific learning disorder was nearly equally distributed in all the 3 groups.

3.2. Demographic and SNAP scores

The ages of the R, NR, and PR groups did not differ from one another ($F = 1.1$, $p = 0.34$). Changes in SNAP scores varied as a function of treatment interval across the R, NR, and PR groups (Table 3). At baseline there were no significant differences between the three groups for any SNAP score. Children in the NR group showed no changes for any SNAP score across treatment intervals. Children in the PR group showed decreased inattention scores after 3, 6, and 12 months of treatment although hyperactivity, combined, and oppositional SNAP scores remained at baseline levels across the 12 months of treatment. Children classified as responders showed decreased SNAP inattention, hyperactivity, combined, and oppositional SNAP scores after 3 months and these changes remained present after 6 and 12 months of treatment.

Table 2
Shows the distribution of the comorbidities of the 37 children with ADHD divided in responders (R), partial responders (PR) and non-responders (NR) for whom data was available after the third month of therapy.

Comorbidity	R	PR	NR
Oppositive Defiant Disorder	3	4	8
Specific learning disorder	4	3	2
Anxiety disorder	1	–	2
Conduct disorder	–	–	1
Language disorder	1	–	–
Generalized learning disorder	–	–	1
Conduct disorder + anxiety disorder	–	–	–
Language disorder + anxiety disorder	1	–	–
Tics + Oppositive Defiant Disorder	1	–	–
None	–	3	2
Total	11	10	16

3.3. QEEG

Fig. 1 presents color coded head maps of Z-absolute power (compared to database of normal children) separately for the R and NR groups at baseline, 6 months, and 12 months following treatment. At baseline responders showed increased frontal/anterior temporal alpha and elevated frontal/anterior temporal delta and theta in comparison to the normal population. Non-responders showed increased power across all frequency bands that were greatest in anterior and central regions. Across the 12 month treatment interval these increased absolute power values decreased in the responders (moved towards normal values), whereas, across these same time intervals the increased absolute power levels remained constant for the non-responders. Fig. 2 shows color coded head maps of the significance of the difference between R and NR children at each electrode location and each frequency band at baseline, 6 months and 12 months after treatment. It should

Table 3
Reports the Anova results at baseline (BL), 6 and 12 months for non-responders and responders of the SNAP-Combined (SNAP-C), SNAP-Hyperactivity (SNAP-H), SNAP-Inattention (SNAP-I) and SNAP-Opposition (SNAP-O) scores, respectively.

	Non-responders		Responders			
	Mean	SD	Mean	SD	F-value	p-Value
SNAP-C						
BL	2.17	0.74	2.51	1.2	0.64	0.43
6 months	2.46	0.54	1.21	0.76	17.9	0.0003
12 months	2.32	1.02	1.20	1.1	3.41	0.08
SNAP-H						
BL	2.15	0.90	2.19	1.5	0.01	0.94
6 months	2.55	0.75	1.04	0.8	22.1	0.0001
12 months	2.10	1.2	0.71	0.9	6.8	0.02
SNAP-I						
BL	2.05	0.40	2.54	1.0	1.4	0.25
6 months	2.50	0.50	1.20	0.8	6.9	0.01
12 months	2.21	0.99	1.51	1.3	1.9	0.32
SNAP-O						
BL	1.56	0.43	1.42	0.54	0.35	0.56
6 months	1.52	0.37	1.07	0.37	7.7	0.01
12 months	2.10	0.29	0.99	0.41	25.0	0.0001

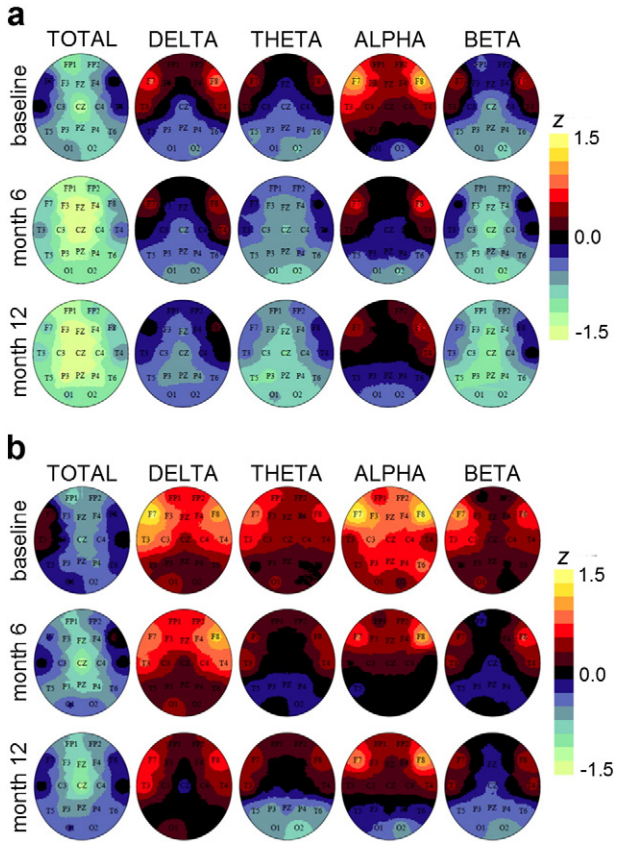

Fig. 1. Shows the average Z-score maps of absolute power for the delta, theta, alpha, and beta frequency bands of the responders and non-responders at baseline, 6 months and 12 months. Z-scores are relative to the normal population with statistical significance at the $p < 0.01$ level equal to a Z-score of 1.96/Square root of N.

be noted that at baseline significant R vs. NR differences involved mainly posterior regions but that by 6 and 12 months were generalized across all locations. Fig. 3 shows color coded head maps of the significance of the difference between baseline and 6 and 12 months after treatment separately for responders and non-responders. Responders showed significant decreases in power for all frequency bands at 6 and 12 months that was greatest in anterior, central, and temporal regions (regions where baseline abnormal findings were present) with no changes in posterior regions. Non-responders showed no changes in

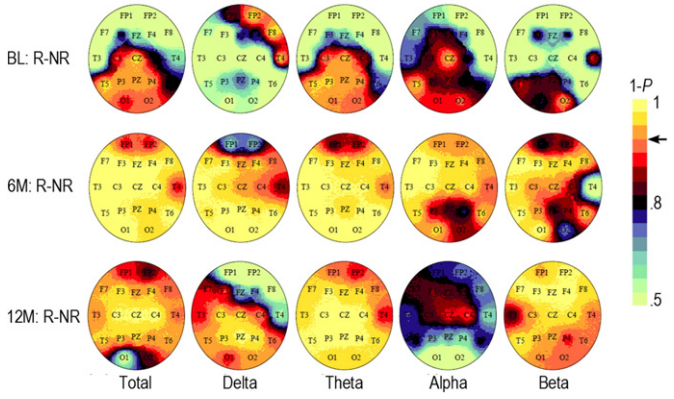

Fig. 2. Shows color coded head maps of the significance of absolute power difference between responders and non-responders at baseline (BL), 6 months (6 M) and 12 months (12 M). The black arrow indicates significance at the $p < 0.005$ level.

absolute power levels after 6 and 12 months of treatment compared to baseline values. Thus, treatment with ATX reduced the frontal QEEG abnormality present in the responders and had no effect upon the QEEG of the non-responders.

3.4. VARETA

Fig. 4a presents VARETA images for the responders at an average single Hertz frequency band of 11.7 Hz, the frequency band with the highest average Z-score relative to the normal population (1.5 to 30 Hz in 0.39 Hz steps). The responders at baseline showed increased activation relative to the normal population in the right middle, superior, and inferior temporal gyrus, in the right insular, in the pre and post central gyrus, in the supramarginal gyrus, in the mid frontal gyrus, in the posterior cingulate region, in the angular gyrus, in the medial frontal gyrus, and the superior parietal lobule. Fig. 4b shows the same VARETA images 12 months after treatment. Abnormal activation has decreased dramatically with significant findings seen only in the lateral, medial, and fronto-orbital gyrus, in the medial frontal gyrus, and the anterior cingulate region. Fig. 5a presents VARETA images at BL for the NR's at 15.2 Hz the frequency value with the greatest average increased Z-score relative to the normal population. Increased activity can be seen in right medial, inferior, and superior temporal gyrus, in the pre and post central gyrus, in the left inferior frontal gyrus, the supramarginal gyrus, in the left medial frontal gyrus, and in the angular gyrus. Decreased activation is present in the latero-medial fronto-orbital gyrus, superior and medial frontal gyrus the anterior cingulate region, the occipito-temporal gyrus and the cerebellum. Fig. 5b shows the same VARETA images 12 months after treatment. It can be seen that increased activity remains present in all areas that showed abnormal activation at baseline. The reduced activation is still present in the occipito-temporal gyrus and the cerebellum.

4. Discussion

In our study Atomoxetine had a positive effect on 21 subjects (55.6%), of which 11 (27.8%) were classified as responders and 10 (27.8%) showed a partial remission of ADHD symptoms (Partial Responders). Responders showed remission of all SNAP symptoms, whereas, the partial responders only showed a decrease in SNAP inattention. These results are in agreement with previous studies reporting that the effect size for atomoxetine treatment in ADHD patients ranges from 0.63 to 0.71 and the response to atomoxetine treatment ranges from 59.5% to 69% while remission ranges from 27% to 28.6% (Weiss et al., 2005; Kelsey et al., 2004; Michelson et al., 2002). 16 subjects, (44.4%) were defined as non-responders with SNAP-C, SNAP-I, and SNAP-O scores increasing and SNAP-I scores remaining at baseline levels.

An expanding literature has demonstrated a relationship between baseline profiles of quantitative Electroencephalogram (QEEG) or differences between baseline, retest profiles and ultimate clinical/treatment outcome (Prichep et al., 1993; Hansen et al., 2003; Pizzagalli et al., 2001; Leuchter et al., 2009a, 2009b). Saletu et al. (2002, 2005) suggested a “key and lock” model where the medication of choice is that which causes changes in brain electrical activity which is opposite to abnormalities seen in the baseline QEEG. Suffin and Emory (1995) conducted a prospective, randomized, multiply blinded, controlled pilot study to test clinical efficacy of the QEEG model, and found that pretreatment QEEG data predicted medication response with high accuracy in treatment resistant child and adolescent depression. In our sample responders to ATX had baseline QEEG alpha excess localized to frontal and anterior temporal regions and these abnormal findings decreased after 6 and 12 months of treatment. Non-responders showed QEEG abnormalities across all frequency bands and across frontal and central regions. These QEEG

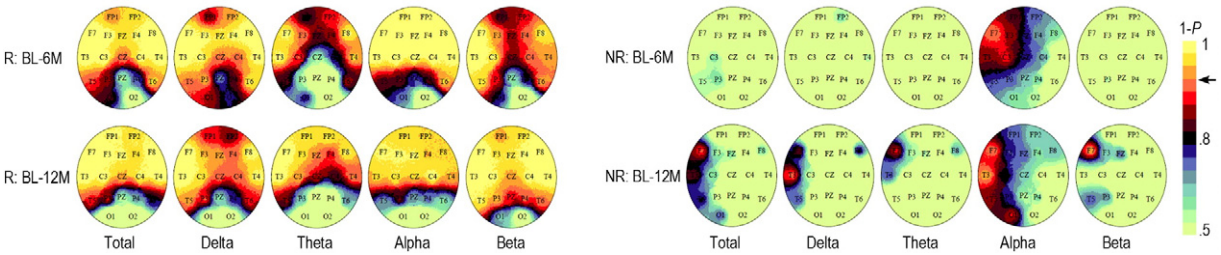

Fig. 3. Shows color coded head maps of the significance of absolute power difference between baseline (BL) and 6 months and 12 months after treatment separately for responders (left panel) and non-responders (right panel). The black arrow indicates significance at the $p < 0.005$ level.

abnormal findings remained constant after 6 and 12 months of treatment.

Many independent laboratories have reported that there are at least 5 different neurophysiological clusters (subtypes) that describe ADHD children. Furthermore, it has been demonstrated that each neurophysiological subtype shows abnormalities in all frequency bands, in terms of absolute, relative power and coherence in prefrontal and frontal areas and there may be a relationship between QEEG subtypes and treatment response. The QEEG profiles shown by the responders and non-responders in this study are consistent with those reported to characterize QEEG subtypes of children with ADHD (Clarke et al., 1998, 2001a, 2001b, 2001c, 2001d, 2002a, 2003a, 2006a; Barry et al., 2003, 2009a; Chabot and Serfontein, 1996; Chabot et al., 1996, 1999, 2001). As described above the responders and non-responders may represent two different QEEG subtypes of ADHD.

QEEG has been shown to have sensitivity and specificity levels varying from 90% to 98% in discriminating normal subjects from those with ADHD and ADHD children from LD children (di Michele et al., 2005; Monastra et al., 1999, 2001; Monastra, 2005). QEEG was also proved useful in the management of treatment response to stimulant medication. A number of studies have investigated changes in the EEG due to stimulant medications with the majority of studies finding that the stimulants result in some normalization of the EEG. Swartwood et al. (1998) and Lubar et al. (1999) failed to find changes in EEG power due to stimulant medication but Chabot et al. (1999) found that 56.9% of a group of children with ADHD showed normalization of the EEG after the administration of a stimulant, while 33.8% remained unchanged and 9.3% showed an increase in EEG abnormality. Loo et al. (1999) found that after the administration of methylphenidate, good responders had decreased theta and alpha but increased beta activity in the frontal regions, while poor responders showed the opposite EEG changes. Clarke et al. (2002b, 2003a, 2003b, 2007) found that stimulant medications resulted in normalization of the EEG with a reduction in theta activity and an increase in beta activity. These results were interpreted as indicating that stimulants acted at a cortical level by increasing arousal although complete normalization was not found in the entire sample.

However, the effects of non-stimulants on the EEG of children with ADHD have not been widely investigated. Clarke et al. (2006b, 2008) examined the EEG characteristics of responders to imipramine hydrochloride (Tofranil®) treatment. The authors reported that the responders to Tofranil© had significantly more absolute and relative theta with deficiencies of relative alpha across all sites compared to controls. Leuchter et al. (2014) used the theta cordance index in predicting atomoxetine treatment response in adult ADHD. Left temporo-parietal cordance in the theta frequency band after one week of treatment was associated with ADHD symptom improvement and quality of life measured at 12 weeks in atomoxetine-treated subjects, but not in those treated with placebo. In the scientific literature there is only one study that investigated the acute treatment effect of 20 mg of atomoxetine in children and adolescents with ADHD (Barry et al., 2007, 2009a). The EEG was recorded after 1 h of ATX administration. Acute atomoxetine administration produced a significant decrease of posterior absolute theta and an increase of absolute beta (especially in right and midline anterior regions). Relative delta was increased, particularly in central regions, and relative beta was globally increased. There were no significant medication effects on absolute alpha activity. However, this study has minimal implications on the long term effects of ATX on QEEG changes. In the present study ATX lead to a normalization of the QEEG's of the responders but had no effect upon the QEEG's of the non-responders.

Our study confirms that children with ADHD at baseline show QEEG abnormalities as reported in the literature and adds new data about the chronic effects of ATX on the QEEG of ADHD children. The effects of therapy are clearly visible at 6 months when R is compared with NR. Differences between R and NR were seen at baseline: the R show greater activity in the right prefrontal and frontal regions compared to the NR in the delta band. Theta activity is greater in the NR in the left temporal and parietal areas. The NR had greater alpha absolute power in central and left temporo-parietal and occipital regions bilaterally. Absolute power in the beta band especially in the posterior regions is higher in

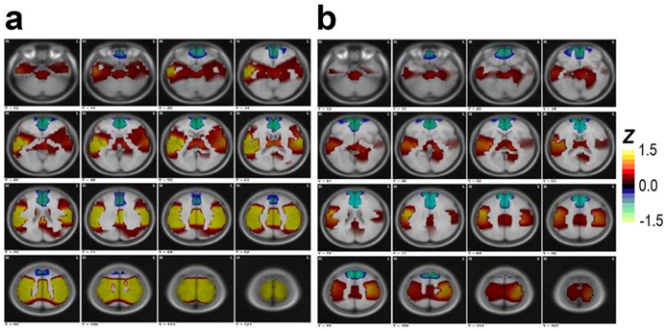

Fig. 4. a: Presents VARETA images at baseline for the responders at an average single Hertz frequency band of 11.7 Hz, the frequency band with the highest average Z-score relative to the normal population. b: Shows the same VARETA images 12 months after treatment.

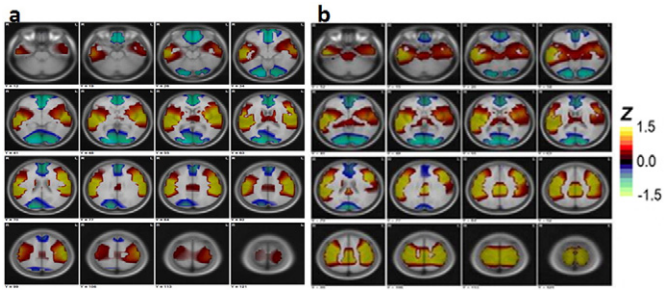

Fig. 5. a: Presents VARETA images at baseline for the non-responders at an average single Hertz frequency band of 15.2 Hz, the frequency range with the greatest average increased Z-score relative to the normal population. b: Shows the same VARETA images 12 months after treatment.

the NR. At 12 months of therapy the R show a normalization of absolute power in all frequency bands while the NR maintain the excess of activity in all frequency bands except the alpha band. The differences between R and NR at 12 months were highly significant especially in the delta band posteriorly, the theta band centrally and the beta band anteriorly.

VARETA source localization proved useful in the current study by indicating the cortical structures which show abnormal function in ADHD children. In a recent paper (Chabot et al., 2015) it was noted that groups of ADHD children and autistic children could be sub-typed based upon the mean frequency bands showing the greatest deviation from normal population. VARETA images calculated at these different frequency values showed consistent anatomical differences from normal that were similar across each subtype of autism and ADHD but that differences persisted between the autistic and ADHD at all frequency levels. ATX responders showed increased activation in right middle, superior, and inferior temporal gyrus, in the right insula, in the pre and post central gyrus, in the supramarginal gyrus, in the mid frontal gyrus, in the posterior cingulate region, in the angular gyrus, in the medial frontal gyrus, and the superior parietal lobe. This increased activation decreased after 6 and 12 months of ATX. Non-responders to ATX showed increased activation in right medial, inferior, and superior temporal gyrus, in the pre and post central gyrus, in the left inferior frontal gyrus, the supramarginal gyrus, in the left medial frontal gyrus, and in the angular gyrus with this increased activation remaining constant despite 12 months of treatment with ATZ. The reduced activation remained the same in the occipito-temporal gyrus and the cerebellum. Similar findings have been reported with different techniques supporting the evidence that these cerebral areas are involved in the pathophysiology of ADHD (Barkley, 2006).

The analysis of sources localization shows that at baseline the brain regions that show an excess of beta activity are the same in R and in NR. This might suggest that subjects with ADHD_C both R and NR share the same structural organization, but what distinguishes the R from NR is the functional organization as it appears by absolute power spectra. The NR continued to have an excess of beta activity and an excess of delta and theta activity.

One of the possible factors of the lack of response to ATX could be the presence of a greater number of ADHD subjects with Oppositional Defiant Disorders (ODD). Recently Chiarenza et al. (2014) reported that subjects with ADHD_C + ODD show abnormal EEG activity in the right anterior cingulate, in the right lateral and medial orbito frontal gyrus, in the alpha and beta bands in comparison to a group of subjects with ADHD_C.

Cortese et al. (2012) recently performed a comprehensive meta-analysis of 55 task-based functional MRI studies of attention deficit hyperactivity disorder. In children, hypoactivation in ADHD relative to comparison subjects was observed mostly in systems involved in executive function (fronto-parietal network) and attention (ventral attentional network). The authors provide evidence that ADHD is a result of dysfunction in multiple neuronal systems involved in higher-level cognitive functions and in sensorimotor processes, including the visual system and the default network. Our VARETA source localization method applied to QEEG, even if recorded with eyes closed and in quiet state, fully confirms these observations and contributes to the understanding of ADHD pathophysiology. It should be noted that the interpretation of VARETA has some pros/cons: it is statistically more robust, diminishes the effect of outliers and increases the chances of regions to become biomarkers. However if the region is big and few voxels are significant, the average can mask those significant voxels activities.

To date there are no studies that demonstrate a clear relationship between clinical profile of subjects with ADHD at “baseline” and response to treatment. Further, a limitation of most studies which have investigated the efficacy of stimulants or SNRI is that response measurements involve subjective teacher and parent ratings (Efron et al., 1997, 2002; Elia et al., 1991) and/or continuous performance tests (CPT) (Efron et al., 1997) without including objective and physiological measurements. Therefore, the questions related to aetiology, pathophysiology, diagnosis and therapy that ADHD imposes remain unresolved. There is a need for more precise and objective formulation of the diagnosis of ADHD, leading the way to more optimal treatment and increase the diagnostic sensitivity to ADHD. Increased understanding of neurophysiological profiles of children with ADHD could offer a refined definition of the pathology and a proper selection of subjects that may take some advantages from treatment optimization selection.

4.1. Study limitation

It should be remembered that the ATX selective inhibition of norepinephrine transporters action mechanism is still largely unknown. Therefore further studies are needed to draw a consistent action profile. Another limitation regards the use of multiple comparisons in analyzing the QEEG absolute power variables. Despite setting the significance level at 0.005 the changes observed in the different EEG frequency bands must be taken with caution although if significance was set at $p < 0.001$ the result interpretation would not change. Caution should also be used due to the relatively small number of responders and non-responders present in this study. Further large N studies should be conducted in order to build discriminative functions that may predict treatment response to ATX.

With these assumptions in mind, the results cannot be considered definitive and further research is necessary to confirm the observed significant differences on the QEEG of ADHD children between responders and non-responders after one year of ATX treatment.

5. Conclusions

We conclude that ADHD children 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 activity in the beta band coupled with increased alpha band power, seems to be related to non-responders and stopping atomoxetine should be considered, especially if there is persistence of elevated alpha and beta and an increase of theta after 3 months of treatment. VARETA showed more widespread abnormality in non-responders than responders. R showed abnormal findings localized to frontal and temporal regions whereas in NR abnormal findings also included more posterior regions.

To our knowledge, this study represents the first tentative attempt to detect objective variables of QEEG of patients with ADHD obtained after one year treatment with ATX. These variables could be used as a predictive index of treatment response to ATX. Waiting for further research to confirm the validity of these results, the prolonged observation of the QEEG variables should be considered as reference point of a certain consistency.

Disclosure

Giuseppe Augusto Chiarenza, Robert Chabot, Robert Isenhart, Luciano Montaldi, Marco Paolo Chiarenza, Maria Grazia Lo Torto, and Leslie S. Prichep within 3 years to the time of data collection had not any institutional or commercial relationship with pharmaceutical companies that might pose a conflict of interest.

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