

EXTENDED REPORT

Auditory P300 event related potentials and serotonin reuptake inhibitor treatment in patients with fibromyalgia

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Background: The P300 components of auditory event related potentials (ERPs) are objective measures related to information and cognitive processing.

Objectives: To assess P300 ERPs in female patients with fibromyalgia (FM) in comparison with healthy age matched controls. To investigate the relationship between P300 potentials and pain threshold levels of patients, and subsequent effect of sertraline treatment on P300 potentials.

Methods: P300 auditory ERPs were studied in 13 untreated female patients with FM and 10 healthy controls matched for age, sex, and education. Pain pressure thresholds and total myalgic scores (TMS) were assessed with an algometer. Patients were evaluated for clinical measures and P300 potentials (recorded from the vertex) at the first visit, and then in the fourth and eighth weeks of sertraline treatment.

Results: Patients with FM had significantly lower P300 amplitudes, but not significantly different P300 latencies, than controls at entry. P300 latencies in patients correlated negatively with TMS ($r_s = -0.79$, $p < 0.01$) and P300 amplitudes correlated significantly with TMS ($r_s = 0.53$, $p < 0.05$). Anxiety and depression scores did not correlate significantly with P300 latencies or amplitudes at the study entry. P300 auditory ERPs had increased amplitudes that had reached nearly the same levels as those of the controls at the eighth week without any significant change in their latencies.

Conclusion: The results show reduced P300 amplitudes in patients with FM. Further studies assessing the relationship between P300 ERPs and neuropsychiatric tests are required for better clarification of the clinical relevance of P300 potentials in FM.

Fibromyalgia (FM) is one of the most common rheumatic diseases, characterised by widespread musculoskeletal pain, fatigue, stiffness, sleep disturbances, and frequent concomitant depression.^{1–4} Additionally, patients with FM often have diminished cognitive performance that affects their personal and professional lives. Objective data on this topic have been published,^{5–9} and a number of cognitive functions using neuropsychiatric tests have been examined. The results generally showed lower⁵ or intact information processing speed^{6,7}, and poor working memory^{5,7,8}, long term memory,^{6,7} or vocabulary⁸ in patients with FM.

P300 (P3) potential is a long latency evoked potential which occurs in response to a consciously attended stimulus or event that can be recorded from scalp electrodes, usually placed in the midline over the frontal, parietal, and central regions of the brain. The P3 component of event related potentials (ERPs) is a positive potential reaching its maximum peak at the parietal site about 300–700 ms after an intrusive stimulus, following a negative N2 wave.^{10,11} In most research work or in laboratories, auditory stimuli are used for P3 generation. The measurement of P3 is performed by quantifying its amplitude (size) and latency (timing). The amplitude (μV) is defined as the voltage difference between the component peak and a prestimulus baseline (N2P3). Latency (ms) is defined as the time from stimulus onset to the point of peak positive amplitude.¹¹

The P3 ERP is a neuroelectric expression of attention allocation, information processing speed, and maintenance of working memory.^{11,12} Variations in P3 amplitude are considered to express the degree to which incoming information is processed and incorporated into the working memory, as well as the context in which the stimulus occurs.^{11–13} P3 latency is a measure of the stimulus classification speed, and increases as the cognitive capability decreases from dementing illness or normal aging in correlation with neuropsychiatric tests that

assess how rapidly subjects can allocate and maintain attentional resources.^{11,12}

A decreased amplitude is believed to reflect poor performance of working memory functions of the brain in correlation with some of the neuropsychiatric tests (that is, with verbal paired association subsets of the Wechsler Memory Scale in schizophrenia, short term visual memory in minor ischaemic stroke).^{14,15} In a recent study assessing the offline (assessment in separate sessions) relationship of ERPs with neuropsychiatric tests, P3 ERPs were found to be related to attentional performance with low working memory demands rather than effortful working memory updating, retrieval from memory stores, or mild cognitive impairment.¹⁶

In this study we assessed P3 auditory ERPs in female patients with FM and compared them with those of healthy controls matched for age, sex, and education. The relationship of P3 potentials with pain threshold levels of the patients and alterations in these potentials with serotonin reuptake inhibitor (SRI) treatment were also evaluated.

PATIENTS AND METHODS

Thirteen female patients with a mean (SD) age of 41.1 (6.3) years (range 30–49) who met the 1990 American College of Rheumatology (ACR)¹ criteria for the classification of FM and 10 healthy female subjects matched for age (37.9 (6.1) years, range 31–49) and education were enrolled. The patients had a

Abbreviations: ACR, American College of Rheumatology; CPs, control points; ERPs, event related potentials; FIQ, Fibromyalgia Impact Questionnaire; FM, fibromyalgia; HARS, Hamilton Anxiety Rating Scale; HDRS, Hamilton Depression Rating Scale; PPT, pain pressure thresholds; SRI, serotonin reuptake inhibitor; TMS, total myalgic scores; TP, tender points; VAS, visual analogue scale

Table 1 P300 potentials of patients with fibromyalgia and controls at the beginning of treatment

	Patients with FM (n=13)		Controls (n=10)	
	Mean (SD)	Range	Mean (SD)	Range
P300 latency (ms)*	330.4 (29.9)	272–365	320.6 (26.2)	264–349
N2P3 amplitude (µV)†	11.3 (5.6)	4.3–20.4	18.5 (5.3)	9.4–25.3

Patients with FM v controls (Mann-Whitney U test): *not significant; †p<0.05.

mean education level of 7.5 (3.1) years (range 5–15) and the controls a mean of 7.8 (3.2) years (range 5–15). The inclusion criteria for the study group comprised a negative history for dementia, cerebrovascular disease, alcohol abuse, psychoactive drug treatment, and other neurological disorders. None of the patients had comorbid psychiatric disorders and none were receiving treatment with antidepressant drugs. The patients who had been using such drugs were only included if they had stopped using them at least three weeks before the study. All subjects gave their informed consent.

Assessing myalgic scores

The pain pressure threshold (PPT) measurements of patients with FM were performed in the same room in the early afternoon with a mechanical algometer. The same doctor carried out all of the measurements and the tests throughout the study. Before the evaluations, subjects were informed of the procedure. Pain threshold was explained as the amount of pressure adequate to induce a sensation of discomfort, and the subjects were warned that the aim was to determine the pain threshold but not pain tolerance.

Eighteen tender points (TPs) accepted by the ACR for FM¹ and three control points (CPs), which were generally agreed upon and used in several previous studies, were evaluated. The three control points were the mid-forehead, the two thirds distal portion of the dominant forearm, and the dominant thumbnail. The apparatus has a force-pressure handle connected to a rubber disk and calibrated in kg/cm². Pressure was increased at a rate of 1 kg/s, after vertically applied upon the TP, and in this course the subjects were asked to state when they felt pain. A positive TP was defined as a point at which the subject had mild or great pain with <4 kg/cm² pressure. The sum of the PPTs of 21 points (18 TPs, 3 CPs) was calculated as the total myalgic score (TMS in kg/cm²).¹⁷

The Hamilton Depression Rating Scale (HDRS)¹⁸ and Hamilton Anxiety Rating Scale (HARS)¹⁹ were used to evaluate the affective condition of patients with FM. The cut off score for mild depression on the HDRS was 27.

Auditory P300 event related potentials

P3 ERPs were recorded with Ag/AgCl electrodes (impedance was held below 5 kOhm) on a Dantec Keypoint (Medtronic, Denmark) device by the same doctor who was unaware of the

subjects' clinical data, in an electromagnetically isolated, sound attenuating room. Subjects lay down on an adjustable examination table with a semitilted headpiece and were allowed to relax. During recordings, subjects were instructed to minimise blinking and to fix their eyes on the wall to reduce eye movements as much as possible. The active electrode was placed at Cz (vertex) and referenced to the linked earlobe according to the international 10–20 system. P3 evoked potentials were generated after a binaurally presented tone discrimination paradigm through a headphone with frequent (85%) tones of 1000 Hz and rare oddball stimuli (15%) of 2000 Hz at 80 dB. Subjects were instructed to count rare stimuli—target tones at 2000 Hz—and report at the end of the session. When there was a discrepancy of >10% hits between the actual number of stimuli and the number reported by the subjects, recordings were repeated. Frequency limits were 0.1–50 Hz and analysis time was a total of one second, including the 100 ms baseline pre-stimulus. Latencies (ms) of the P3 peak and amplitudes (µV) of P3 were recorded.

Patients were administered the Turkish version of the Fibromyalgia Impact Questionnaire (FIQ)²⁰ after measurements of the ERPs, PPTs, HDRS, HARS at entry and in the fourth and eighth weeks of treatment (sertraline 100 mg daily).

Statistics

The data were analysed on a personal computer using the statistical package for social sciences (SPSS) software. Mann-Whitney U test was used for intergroup comparisons. Patients' consecutive measurements were compared using the Wilcoxon test. Values were correlated with Spearman rank correlation coefficients. A two tailed p<0.05 was considered to be significant.

RESULTS

The entry measurements of P3 latencies of patients were not significantly different, whereas P3 amplitudes were significantly lower than those of the controls (table 1). Table 2 summarises three follow up measurements of TMS, FIQ-5, FIQ-6, HDRS, HARS and P300 potentials of the patients. A significant improvement was found in TMS, FIQ-5, FIQ-6, HDRS, HARS, and P3 amplitudes between their measurements at entry and at the end of eighth weeks of treatment (table 2). P3 latency

Table 2 First, second (fourth week), and third (eighth week) measurements of total myalgic score (TMS), Fibromyalgia Impact Questionnaire items (FIQ-5 and FIQ-6), the Hamilton Depression Rating Scale (HDRS), Hamilton Anxiety Rating Scale (HARS), P300 latency, and amplitudes. Comparisons were performed using Wilcoxon test

	Entry I	4th Week II	8th Week III	p I v II	p I v III
TMS	83.5 (9.5)	84.1 (8.6)	87.1 (7.6)	NS	<0.05
FIQ-5 pain (VAS)	7.0 (1.0)	5.0 (1.7)	4.3 (1.2)	0.02	0.002
FIQ-6 fatigue (VAS)	7.3 (1.5)	5.4 (2.3)	5.0 (2.4)	0.02	0.005
HARS	24.2 (7.3)	16.5 (9.0)	13.8 (8.6)	0.02	0.002
HDRS	21.2 (5.2)	13.9 (6.4)	11.7 (6.2)	0.02	0.002
P300 latency (ms)	330.4 (29.9)	327.3 (33.1)	335.6 (23.3)	NS	NS
N2P3 amplitude (µV)	11.3 (5.6)	13.7 (6.3)	16.7 (5.7)	NS	0.009

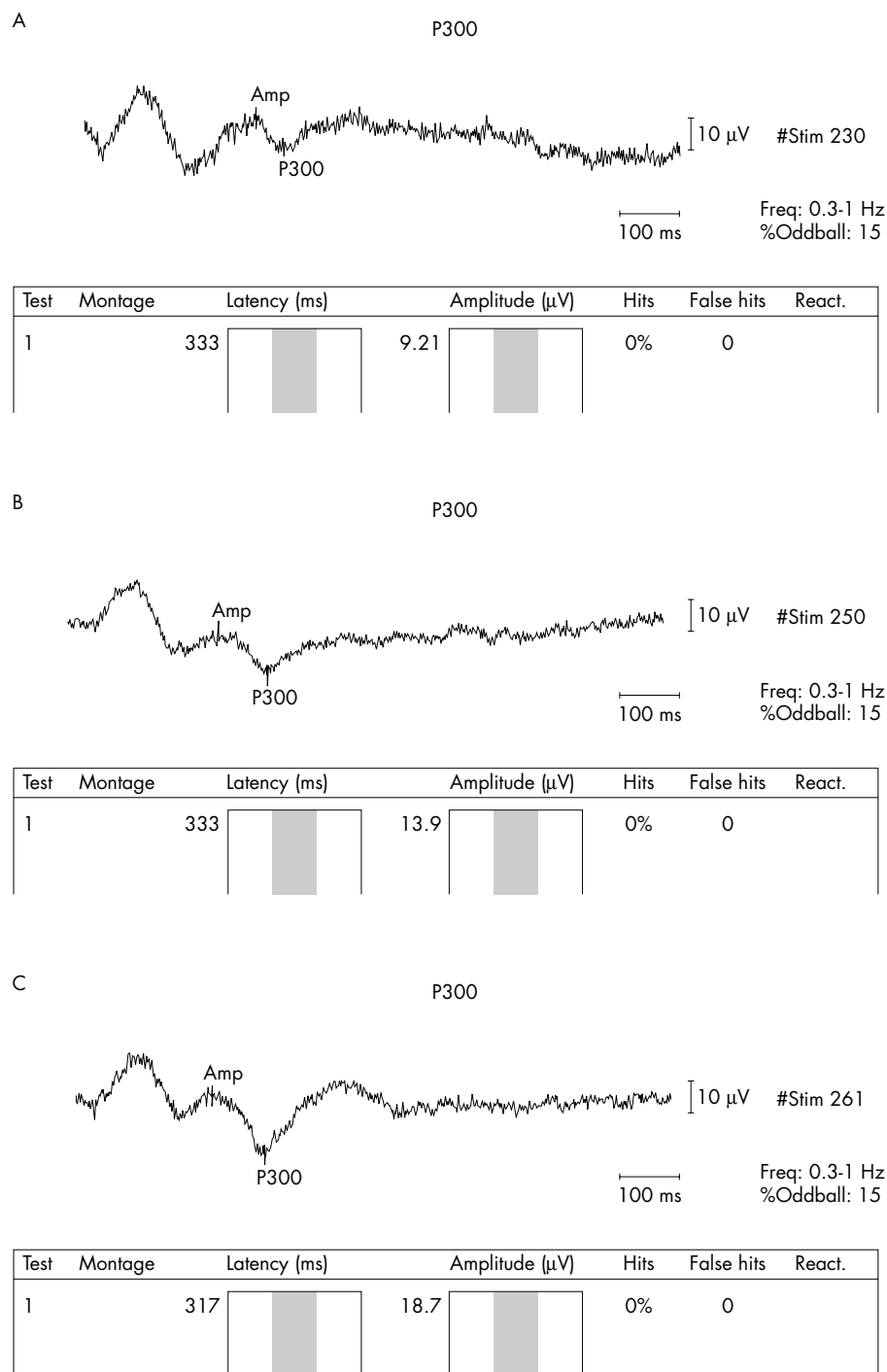


Figure 1 (A) First, (B) second, and (C) third measurements of P300 response to target tones of the same patient recorded from the Cz electrode.

did not change significantly with treatment, but amplitudes significantly improved after an eight week course of treatment with sertraline, almost reaching those of the controls (fig 1).

Relationship of measurements to P3 potentials at study entry

Significant correlation was found between P3 potentials and TMS (latency, $r_s = -0.79$, $p < 0.01$; amplitude, $r_s = 0.53$, $p < 0.05$). Nevertheless, P3 potentials did not correlate with FIQ-5 (pain-visual analogue scale (VAS) scores), and FIQ-6 (fatigue-VAS scores), or HARS and HDRS.

DISCUSSION

Patients with FM usually complain of decline in their everyday cognitive functions. They often have trouble in remembering

things and are unable to concentrate on demanding tasks; this sometimes is more disturbing and disabling than their pain.^{8,9} Most patients are often unable to plan and execute daily work as they feel that they are in a “daze” or “mental fog”—so called “fibrofog”—in which connecting scenes to each other is difficult.^{21,22} They complain of failing even in simple daily tasks, such as cooking, driving, or shopping without missing items on their shopping list, and complain of spending, consequently, much more time on tasks because of forgetfulness.

The P3 component of ERPs is a repeatable, relatively inexpensive, and useful method for the assessment of cognitive ability in normal subjects as well as in patients with neuropsychiatric disorders.^{11,12,23} This method of evaluating cognitive functions is reliable from test to test, and its

variability is highly comparable and sometimes better than routinely employed biomedical assays like cholesterol, glucose, or haemoglobin measurements.^{12-23,24} P3 measurements have some advantages over neuropsychometric tests, in that they are less prone to practice variations and can be performed in a "blinded" manner.²⁵ However, the usefulness of P3 has been restricted because of contributing environmental factors or "biological determinants" or lack of standardised measurement protocols between laboratories.^{11,12,26} For example, amplitudes may be influenced by age of the subject, time of day, season of the year, or recently ingested food and personality type of the subject, whereas latency may be influenced by age, heart rate, and body temperature.²⁷⁻²⁹ Some reports suggest that these effects do not basically restrict the clinical utility of P3 and greater sensitivity could be gained by taking into account these contributing "biological determinants" in the research environment.^{12,27,30,31}

Park *et al* assessed cognitive functions by information processing, recognition memory, working memory function, free recall, verbal fluency, and vocabulary in patients with FM in comparison with age and education matched controls and education matched older controls.⁸ Patients with FM had a poorer performance in all these measures, with the exception of processing speed, than the controls matched for age and education. Patients with FM also had poorer vocabulary than older controls. Additionally, impaired cognitive performance in patients with FM has been found to correlate with pain—measured with Arthritis Impact Measurement Scales—but not with depression or anxiety scores. Similar results have been previously reported by Grace and coworkers, who found an intact speed of processing but decreased working memory and long term memory that correlated with pain scales.⁷

We found no difference in P3 latency, but reduced amplitudes in patients with FM with respect to controls matched for age and education. Significant correlation was also found between P3 potentials and TMS but not with HARS or HDRS. These results should be considered together with previous results⁶⁻⁸ because it has been suggested that P3 latency reflects information processing speed and P3 amplitudes express memory functions more generally.^{11,12}

Gervais and coworkers suggested that incomplete effort and potential exaggeration of cognitive deficits had a role in the assessment of patients with FM, particularly those who claimed medicolegal benefits.³² It is crucial to be aware of response bias during the assessment of memory impairment in FM, especially when there is a disability claim, and study groups should consist of subjects without medicolegal incentives. Similar suspicions about cognitive testing in FM have been put forward by Leavitt and colleagues.²¹ Assessment of P3 potentials has the advantage of being free of possible exaggeration and response bias, but does not give as much detailed information about cognitive functions—that is, verbal fluency, verbal knowledge, or vocabulary, as neuropsychiatric tests.

Another important result of our study was the improvement in P3 amplitudes, but without any change in P3 latencies, as sertraline treatment was given. Previous limited data point out that sertraline treatment had no effect on cognitive function tests in a variety of clinical conditions other than FM.^{33,34} However, Sanz and coworkers obtained increased P3 amplitudes and unchanged P3 latencies with SRI treatment in obsessive-compulsive disorder.³⁵ Serotonin (5-hydroxytryptamine) modulates brain electrophysiological activity³⁶ and, recently, the effect of acute tryptophan depletion on auditory ERPs has been investigated in bipolar disorders.³⁷ Young *et al* showed that acute tryptophan depletion caused reduced amplitudes of the N1P2 and P3 components of the auditory evoked potentials in bipolar patients, especially in the frontal and central scalp areas.³⁷ In our study design it is difficult to estimate the real mechanism of action of sertraline on P3 potentials because significant clinical improvement on

pain, fatigue, or depression scales was also achieved with the treatment. It is unclear whether the effect of sertraline on P3 potentials was related to its serotonergic activity in the central nervous system or to the improvement in clinical parameters, or whether it could solely be attributed to its placebo effect.

In conclusion, our results showed that P3 amplitudes were reduced in patients with FM in comparison with controls matched for age, sex, and education. We emphasise that these data should be followed up in further studies with a broader series of patients with FM—assessing the relationship of P3 ERPs and neuropsychiatric tests in an on line or off line design to ascertain the clinical relevance of P3 potentials in FM.

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REFERENCES

- 1 Wolfe F, Smythe HA, Yunus MB, Bennet RM, Bombardier C, Goldenberg DL, *et al*. The American College of Rheumatology 1990 criteria for the classification of fibromyalgia. *Arthritis Rheum* 1990;33:160-72.
- 2 Clauw DJ. Fibromyalgia. In: Ruddy S, Harris ED, Sledge CB, eds. *Kelly's textbook of rheumatology*. 6th ed. Philadelphia: Saunders, 2001:417-27.
- 3 Ozgcocmen S, Cimen OB, Ardicoglu O. Relationship between chest expansion and respiratory muscle strength in patients with primary fibromyalgia. *Clin Rheumatol* 2002;21:19-22.
- 4 Gur A, Karakoc M, Nas K, Cevik R, Denli A, Sarac J. Cytokines and depression in cases with fibromyalgia. *J Rheumatol* 2002;29:358-61.
- 5 Sletvold H, Stiles TC, Landro NI. Information processing in primary fibromyalgia, major depression and healthy controls. *J Rheumatol* 1995;22:137-42.
- 6 Landro NI, Stiles TC, Sletvold H. Memory functioning in patients with primary fibromyalgia and major depression and healthy controls. *J Psychosom Res* 1997;42:297-306.
- 7 Grace GM, Nielson WR, Hopkins M, Berg MA. Concentration and memory deficits in patients with fibromyalgia syndrome. *J Clin Exp Neuropsychol* 1999;21:477-87.
- 8 Park DC, Glass JM, Minear M, Crofford LJ. Cognitive function in fibromyalgia patients. *Arthritis Rheum* 2001;44:2125-33.
- 9 Glass JM, Park DC. Cognitive dysfunction in fibromyalgia. *Curr Rheumatol Rep* 2001;3:123-7.
- 10 Tachibana H, Toda K, Sugida M. Age-related changes in attended and unattended P3 latency in normal subjects. *Int J Neurosci* 1992;66:277-84.
- 11 Polich J. P300 clinical utility and control of variability. *J Clin Neurophysiol* 1998;15:14-33.
- 12 Polich J, Herbst KL. P300 as a clinical assay: rationale, evaluation and findings. *Int J Psychophysiol* 2000;38:3-19.
- 13 Dochin E, Coles MGN. Is the P300 component a manifestation of context updating? *Behav Brain Sci* 1988;11:357-74.
- 14 Nagasawa T, Kamiya T, Kawasaki Y, Higashima M, Urata K, Sakai N, *et al*. The relationship between auditory ERP and neuropsychological assessment in schizophrenia. *Int J Psychophysiol* 1999;34:267-74.
- 15 Korpelainen JT, Kauhanen ML, Tolonen U, Brusin E, Mononen H, Hillunen P, *et al*. Auditory P300 event related potential in minor ischemic stroke. *Acta Neurol Scand* 2000;101:202-8.
- 16 Portin R, Kovala T, Polo-Kantola P, Revonsuo A, Muller K, Matikainen E. Does P3 reflect attentional or memory performance, or cognition more generally? *Scand J Psychol* 2000;41:31-40.
- 17 Catal SA, Erdem HR, Okumus M, Ozgcocmen S, Yorgancioglu ZR. The measurement of pain pressure threshold in patients with rheumatoid arthritis. *Pain Clinic* 2000;12:187-91.
- 18 Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry* 1960;23:56-62.
- 19 Hamilton M. The assessment of anxiety states by rating. *Br J Med Psychol* 1959;32:50-5.
- 20 Sarmer S, Ergin S, Yavuzer G. The validity and reliability of the Turkish version of the Fibromyalgia Impact Questionnaire. *Rheumatol Int* 2000;20:9-12.
- 21 Leavitt F, Katz RS, Mills M, Heard AR. Cognitive and dissociative manifestations in fibromyalgia. *J Clin Rheumatol* 2002;8:77-84.
- 22 Starlanyl DJ, Copeland ME. *Fibromyalgia and chronic myofascial pain: a survival manual*. 2nd ed. Oakland, CA: New Harbinger Publications, 2001:199-208.

- 23 **Segalowitz S**, Barnes K. The reliability of ERP components in the auditory oddball paradigm. *Psychophysiology* 1993;30:451-9.
- 24 **Taghavy A**, Kugler CFA. The pattern flash elicited P300 potentials (PF-P300): a new method for studying cognitive processes of the brain. *Int J Neurosci* 1988;38:179-88.
- 25 **Weissenborn K**, Wiltfang J, Schmidt FW, Kunkel H. Neurophysiological assessment of early hepatic encephalopathy. *Electroencephalogr Clin Neurophysiol* 1990;75:289-95.
- 26 **Polich J**, Kok A. Cognitive and biological determinants of P300: an integrative review. *Biol Psychol* 1995;41:103-46.
- 27 **Polich J**. P300 in clinical applications. Meaning, method and measurement. *Am J EEG Technol* 1991;31:201-31.
- 28 **Geisler M**, Polich J. P300 and time of day: circadian rhythms, food intake and body temperature. *Biol Psychol* 1990;31:1-20.
- 29 **Geisler M**, Polich J. P300, food consumption, and memory performance. *Psychophysiology* 1992;29:76-85.
- 30 **Kugler CFA**, Taghavy A, Platt D. The event-related P300 potential analysis of cognitive human brain aging: a review. *Gerontology* 1993;39:280-303.
- 31 **Kugler CFA**, Petter J, Platt D. Age-related dynamics of cognitive brain functions in humans: an electrophysiological approach. *J Gerontol Biol Sci* 1996;51A:B3-16.
- 32 **Gervais RO**, Russell AS, Green P, Allen LM III, Ferrari R, Pieschl SD. Effort testing in patients with fibromyalgia and disability incentives. *J Rheumatol* 2001;28:1892-9.
- 33 **Newhouse PA**, Krishnan K, Doraiswamy P, Richter EM, Batzar ED, Clary CM. A double-blind comparison of sertraline and fluoxetine in depressed elderly outpatients. *J Clin Psychiatry* 2000;61:559-68.
- 34 **Meador KJ**. Cognitive side effects of medications. *Neurol Clin* 1998;16:141-55.
- 35 **Sanz M**, Molina V, Martin-Loeche M, Calcedo A, Rubia FJ. Auditory P300 event-related potential and serotonin reuptake inhibitor treatment in obsessive-compulsive disorder patients. *Psychiatry Res* 2001;101:75-81.
- 36 **Seifritz E**, Moore P, Trachsel L, Bhatti T, Stahl SM, Gillin JC. The 5-HT1A agonist ipsapirone enhances EEG slow wave activity in human sleep and produces a power spectrum similar to 5-HT2 blockade. *Neurosci Lett* 1996;209:41-4.
- 37 **Young AH**, Hughes JH, Marsh VR, Ashton CH. Acute tryptophan depletion attenuates auditory event related potentials in bipolar disorder: a preliminary study. *J Affect Disord* 2002;69:83-92.

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