MISMATCH NEGATIVITY AND PERSONALITY TRAITS IN CHRONIC PRIMARY INSOMNIACS

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INTRODUCTION

The prevalence of sleep disorders is about 20% of the population (1). Among patients affected, sufferers from primary insomnia associated with functional or psychogenic causes can be separated from those whose insomnia is associated with organic brain lesions evidenced by neuroimaging techniques. However, the exact pathogenesis of primary insomnia is still unclear. The anteroventral and dorso-medial thalamic nuclei, which are interconnected with the limbic, paralimbic and frontal cortical regions, are important sites of sleep-wake regulation (2). In a neurophysiological study, the cerebral blood flow was prominently decreased in the prefrontal cortex during slow wave sleep in healthy volunteers (3), while in fatal familial insomnia, a diffuse degeneration has been found through the thalamo-cortical pathways, especially the thalamus (4).

In general, since the thalamo-(fronto)cortical (TFC) circuit has prominent anatomical connections that control volitional and psy-
chomotor behaviors, emotion and personality (5), the increased Depression, arousal and Neuroticism levels found in insomniacs (6) might suggest dysfunctions of these brain areas.

To obtain more evidence of TFC circuit involvement in chronic primary insomnia, neurophysiological study of auditory mismatch negativity (MMN), an event-related potential (ERP), might be another suitable approach. This potential can be elicited by any infrequent differentiable change in a repetitive sound. Recent studies show that MMN has at least two contributors (7): a) the supratemporal auditory cortex with contributions from the auditory thalamus and hippocampus; b) the frontal cortex which might underlie involuntary orienting of attention towards devianee.

If the TFC circuit plays a hyperactive role in chronic primary insomnia, we would expect to find an increased MMN amplitude in affected subjects, as well as correlations between the amplitude and some personality traits. Therefore, we conducted MMN and personality studies in a group of chronic primary insomniacs and in a group of healthy volunteers.

MATERIALS AND METHODS

Subjects

This study was carried out on 51 subjects: 23 outpatients (12 women, 11 men; aged 30.2 years ± 7.0 SD) diagnosed according to DSM-IV criteria (8) as having chronic primary insomnia; 28 healthy volunteers (19 women, 9 men; aged 27.2 ± 5.0) recruited among students, hospital staff or paid volunteers. There were no statistically significant differences between age and gender distribution in the subject groups. The mean duration of the sleep disorder in patients was 6.5 months (range: 3 - 30 months). Patients had no supplementary sleep during the day. They might have dreams during sleep, but seldom had nightmares or night terrors. With reference to the characteristics of the sleep disorders, 8 out of 23 sufferers were categorized in a subgroup having difficulty in falling asleep (DFS), the remaining 15 in a subgroup having early awakening or unrefreshing sleep or both (EUB). Two patients in the EUB subgroup had a sleepwalking history during childhood. It was also ascertained that patients had not used neuroleptics or anti-depressants for at least 1 week prior to the test. In addition, no subject presented hearing impairment, drug/alcohol abuse. All the subjects gave their informed consent to the study.

Neurophysiological test

Subjects were seated comfortably in an armchair in a quiet room. Binaural tone stimuli (50 ms in duration with a rise-fall time of 10 ms) were delivered through earphones at 2 KHz and an interstimulus interval of 0.625 s (1.6 Hz). Frequent tones (90%) had a 70 dB sound pressure level; deviant tones (10%) had an 80 dB level. Holding a pen in the dominant hand, subjects were instructed to arrange a series of 7 randomized digits (selected from 0 to 9) in ascending order. We employed this approach in order to divert the subjects’ attention from the auditory stimuli.

The ERPs were recorded with cup electrodes placed at midline Fz, Cz and Pz (10-20 system) and referenced to two linked cup electrodes placed at both sides of the mastoid. The potentials were amplified and averaged with a Nihon Kohden Neuropack-sigma device using a 20 Hz high-cut and 0.5 Hz low-cut filter. The sampling epoch was 100 ms pre-stimulus and 400 ms post-stimulus.

Fifty responses were analyzed for each trace. Since MMN typically overlaps with N1 (80-120 ms) and P2 (150-250 ms) deflections, we chose to analyze the difference waves obtained by subtracting frequent tone ERPs from deviant tone ERPs as proposed (7). The subtracted traces were analyzed in terms of peak
latency and baseline-to-peak amplitude of the maximal negative deflection determined by visual inspection of each average recording within latency ranges of 80 to 250 ms.

Questionnaires

Before the neurophysiological test, each subject was asked to answer 3 questionnaires on-site in another quiet room. A brief overview of each questionnaire is given below:

1) Plutchik-van Praag's depression inventory (PVP). This contains 34 items; each item has three scale points (0, 1, 2) which correspond to increasing depressive tendencies. Subjects show “possible depression” if they score between 20 and 25, and depression if they score more than 25. The internal reliability of this inventory is 0.93 (9);

2) Zuckerman's sensation seeking scales (SSS; form V, 40 items). One point is given for each item chosen corresponding to sensation seeking. The test provides four scales with ten items each, i.e., Thrill and adventure seeking; Experience seeking; Disinhibition; and Boredom susceptibility. The total score in each subject was calculated as the sum of the four scale scores. The internal reliabilities of these scales range from 0.56 to 0.82 (10);

3) Zuckerman-Kuhlman’s Personality Questionnaire (ZKPQ). One point is given for each item chosen corresponding to personality traits. The test provides five measurements: a) Impulsive sensation seeking (19 items), composed of two units, i.e., 8 items of Impulsivity and 11 items of General sensation seeking which is compared to the SSS described above; b) Neuroticism-anxiety (19 items); c) Aggression-hostility (17 items); d) Activity (17 items); and e) Sociability (17 items). The internal reliabilities of these scales range from 0.72 to 0.86. In this questionnaire, ten items of another scale (Infrequency or Lie) were randomly inserted as a test validity indicator for individuals (11).

Statistical analysis

MMN latencies or amplitudes obtained at three midline electrode sites in the two groups and those in the two patient subgroups were analyzed by 2-way ANOVA. Once the main effect had been obtained and indicated that the latencies/amplitudes were different at different electrode sites or in (sub)groups, post-hoc analysis by the independent Student’s *t* test plus Bonferroni’s correction was employed. The PVP, SSS and ZKPQ scores obtained in the two subject groups and in the two patient subgroups were submitted to the non-parametric Mann-Whitney U test. Spearman’s rank order correlation was used to search for possible relations between MMN latencies/amplitudes, PVP, SSS, ZKPQ scores, and subjects’ ages. A *p* value less than 0.05 was considered to be significant.

RESULTS

During the study procedure, no subject reported drowsiness. Fifty-one subjects completed the neurophysiological tests; 25 healthy subjects and 23 patients filled out the questionnaires.

The subtracted traces showed clear MMN responses in each subject. Illustrative recordings obtained in a healthy subject and a patient are shown in Fig. 1 (see over). In three electrode sites, longer MMN latencies (main effect, *F* = 4.79, *p* = 0.033) and higher amplitudes (main effect, *F* = 4.41, *p* = 0.041) were found in insomniacs. However, only differences in latency at Pz (*p* = 0.042) and in amplitude at Fz (*p* = 0.032) reached the level of statistical significance (Table I, see over). On the other hand, there were no significant differences in either MMN latencies or amplitudes between the two patient subgroups (Table I).

All the healthy subjects scored less than 20 on the PVP depression scales; 4 patients scored between 20-25 and were regarded as having
Fig. 1 - Illustrations (each trace 50 responses) of auditory event-related potentials by frequent and deviant tones, and the respective potential differences (i.e. the subtracted responses, dashed lines) in a healthy control and a patient with insomnia. Asterisks indicate potentials of mismatch negativity.

Table I - Latencies and amplitudes (mean ± s.d.) of mismatch negativity (50 responses, after subtraction) at three midline electrode sites (Fz, Cz and Pz) in healthy controls, chronic primary insomniacs, and respectively in the two insomniac subgroups (DFS and EUB).

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Fz</th>
<th>Cz</th>
<th>Pz</th>
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<tbody>
<tr>
<td><strong>Latency (ms)</strong></td>
<td></td>
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<tr>
<td>Controls (no. = 28)</td>
<td>160.0 ± 43.8</td>
<td>161.2 ± 39.3</td>
<td>161.2 ± 33.9</td>
</tr>
<tr>
<td>Insomniacs (no. = 23)</td>
<td>186.0 ± 46.5</td>
<td>188.4 ± 44.8</td>
<td>191.3 ± 46.0*</td>
</tr>
<tr>
<td>– DFS (no. = 8)</td>
<td>195.8 ± 59.1</td>
<td>202.4 ± 57.2</td>
<td>201.8 ± 64.1</td>
</tr>
<tr>
<td>– EUB (no. = 15)</td>
<td>178.0 ± 40.0</td>
<td>178.2 ± 36.9</td>
<td>182.9 ± 35.0</td>
</tr>
<tr>
<td><strong>Amplitude (µV)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controls (no. = 28)</td>
<td>-1.2 ± 2.7</td>
<td>-1.9 ± 2.9</td>
<td>-0.7 ± 3.0</td>
</tr>
<tr>
<td>Insomniacs (no. = 23)</td>
<td>-3.7 ± 4.3*</td>
<td>-2.8 ± 4.0</td>
<td>-2.0 ± 2.6</td>
</tr>
<tr>
<td>– DFS (no. = 8)</td>
<td>-4.7 ± 4.8</td>
<td>-5.0 ± 4.8</td>
<td>-3.6 ± 1.8</td>
</tr>
<tr>
<td>– EUB (no. = 15)</td>
<td>-3.6 ± 3.4</td>
<td>-0.2 ± 2.3</td>
<td>-1.4 ± 2.2</td>
</tr>
</tbody>
</table>

Abbreviations: DFS = difficulty in falling asleep; EUB = early awakening or unrefreshing sleep or both. *p < 0.05, insomniacs vs controls.
“possible depression”, 11 patients scored more than 25 and were considered depressed. On average, insomniacs (23.7±10.9) gave significantly higher (p = 0.00001) depression scores than healthy controls (9.1±4.8). There was a trend (non-significant) of higher PVP scores in the EUB subgroup (25.0±9.7) than that in the DFS subgroup (19.9±12.0). In general, insomniacs scored higher on the items of Neuroticism-anxiety (p = 0.0059) and Impulsivity (p = 0.015) but lower on Thrill and adventure seeking (p = 0.005). There were no statistically significant differences in personality scores between the two patient subgroups except that the Aggression-hostility was elevated (p = 0.013) in the EUB with respect to the DFS subgroup (Table II).

In healthy subjects, MMN amplitudes at Fz (no. = 25, r = -0.40, p = 0.046), Cz (no. = 25, r = -0.63, p = 0.0008) and Pz (no. = 25, r = -0.47, p = 0.017) were negatively correlated with Experience seeking; while the amplitude at Fz (no. = 25, r = 0.42, p = 0.035) was positively correlated with Neuroticism-anxiety. However, none of these correlations were replicated in patients. Nonetheless, MMN amplitudes at Fz (no. = 23, r = 0.64, p = 0.0011) and at Cz (no. = 23, r = 0.44, p = 0.036) were positively correlated with the PVP depression score in patients. The MMN amplitude at Fz in patients was positively correlated with Impulsivity (no. = 23, r = 0.43, p = 0.039) which contributed to the positive correlation between the amplitude and Impulsive sensation seeking (no. = 23, r = 0.46, p = 0.027).

DISCUSSION

In this study, MMN amplitudes were higher at Fz and Cz, especially in chronic primary insomniacs (Table I) which is in accordance with the suggestion that Fz is a good location to measure MMN (7). When concentrated on Fz, the MMN latency tended to be longer but not significantly so; in contrast, its amplitude was

<table>
<thead>
<tr>
<th>Questionnaires</th>
<th>Controls (no. = 25)</th>
<th>Insomniacs (no. = 23)</th>
<th>DFS (no. = 8)</th>
<th>EUB (no. = 15)</th>
</tr>
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<tr>
<td><strong>SSS</strong></td>
<td></td>
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<tr>
<td>Thrill and adventure seeking</td>
<td>6.4 ± 2.5</td>
<td>4.0 ± 2.4*</td>
<td>4.9 ± 3.0</td>
<td>3.9 ± 2.3</td>
</tr>
<tr>
<td>Experience seeking</td>
<td>4.0 ± 1.9</td>
<td>3.1 ± 1.7</td>
<td>3.6 ± 1.7</td>
<td>2.7 ± 1.6</td>
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<tr>
<td>Disinhibition</td>
<td>2.8 ± 1.8</td>
<td>2.9 ± 2.1</td>
<td>2.0 ± 1.1</td>
<td>3.3 ± 2.4</td>
</tr>
<tr>
<td>Boredom susceptibility</td>
<td>1.7 ± 1.5</td>
<td>2.5 ± 1.7</td>
<td>2.1 ± 1.4</td>
<td>3.0 ± 2.0</td>
</tr>
<tr>
<td>TOTAL</td>
<td>14.8 ± 5.2</td>
<td>12.5 ± 5.1</td>
<td>12.6 ± 5.7</td>
<td>12.9 ± 5.6</td>
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<tr>
<td><strong>ZKPQ</strong></td>
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<tr>
<td>Impulsive sensation seeking</td>
<td>8.2 ± 3.0</td>
<td>8.8 ± 3.2</td>
<td>8.9 ± 2.0</td>
<td>8.9 ± 4.0</td>
</tr>
<tr>
<td>– Impulsivity</td>
<td>2.7 ± 1.6</td>
<td>4.0 ± 1.9*</td>
<td>3.5 ± 2.2</td>
<td>4.5 ± 1.9</td>
</tr>
<tr>
<td>– General sensation seeking</td>
<td>5.5 ± 2.1</td>
<td>4.8 ± 2.3</td>
<td>5.4 ± 1.9</td>
<td>4.4 ± 2.5</td>
</tr>
<tr>
<td>Neuroticism-anxiety</td>
<td>7.3 ± 2.8</td>
<td>11.7 ± 4.6*</td>
<td>12.5 ± 3.6</td>
<td>10.9 ± 4.8</td>
</tr>
<tr>
<td>Aggression-hostility</td>
<td>6.3 ± 2.7</td>
<td>7.8 ± 3.7</td>
<td>5.3 ± 3.1</td>
<td>9.9 ± 3.3**</td>
</tr>
<tr>
<td>Activity</td>
<td>8.7 ± 2.7</td>
<td>7.6 ± 3.4</td>
<td>9.6 ± 4.0</td>
<td>7.0 ± 3.1</td>
</tr>
<tr>
<td>Sociability</td>
<td>7.3 ± 2.4</td>
<td>7.3 ± 3.8</td>
<td>8.4 ± 3.2</td>
<td>6.9 ± 3.8</td>
</tr>
</tbody>
</table>

Abbreviations: DFS = difficulty in falling asleep; EUB = early awakening or unrefreshing sleep or both. *p < 0.05, insomniacs vs controls; **p < 0.05, EUB vs DFS.
significantly higher in patients. As expected, patients showed increased Neuroticism-anxiety and Depression. The increased Aggression-hostility scores in the EUB subgroup of patients were also in line with the finding that some insomnia sufferers, especially sleepwalkers, have higher levels of outward expression of aggression (12). However, one should bear in mind that in our study, there was a limitation in that we did not perform the nocturnal polysomnographic recordings or multiple sleep latency tests in our patients. The possible relationships between the MMN/personality and the polysomnography or the multiple sleep latency tests are thus unknown. Nevertheless, these ideas merit further investigation.

MMN is induced by initiation of a sequence of brain events which underlie attention switching in response to an occasional stimulus change (7). Anxiety, as an alarm system, also influences attention switching (13). Consistently, Neuroticism-anxiety was positively correlated with MMN amplitude at Fz in our healthy volunteers. MMN latency can be interpreted as the time needed by the memory comparison process to detect the stimulus change; meanwhile its amplitude reflects an automatic discrimination accuracy or sensitivity to a small stimulus change (7). Impulsivity increases sensitivity to signal changes (13), and it might be associated with a major process underlying short-duration memory retention in the cortex. This might be the case in chronic insomniacs particularly, whose higher Impulsivity was positively correlated with MMN amplitude.

The auditory evoked N1 amplitude as well as latency changes are correlated with SSS that measure a subject’s arousal levels (14). The early ERP components like MMN, on the other hand, can reflect the level of arousal to a deviant stimulus (7). Arousal levels higher than the optimal one would lead a subject to cease sensation seeking (10), and this might explain the negative correlations between Experience seeking personality and MMN amplitude found in our healthy subjects. Although these correlations were not reproducible in patients, in accordance with the literature, the insomniacs were highly aroused (the higher MMN amplitude, Table I) and showed a trend to score lower in Experience seeking (Table II).

Increased depression distracts a subject’s attention from performing the required task as exemplified by the “oddball” ERP studies in which depressives have reduced P3 amplitudes (15). In the present study, in which the required task was to arrange a series of randomized digits in order, the response to the auditory deviant stimulus was however, augmented in insomniacs. This might underlie the positive correlations between MMN amplitudes at Fz/Cz and Depression. The coexistence of decreased Thrill and adventure seeking and increased Neuroticism-anxiety was also found in insomniacs. These two personality traits are indeed negatively correlated with each other (11) as the sports-related items in sensation seeking scales are weakly related to Neuroticism but are often included in Thrill and adventure seeking (10).

Both MMN amplitude and personality results in the present report suggest a TFC neuronal hyperactivity in chronic primary insomniacs. It has been shown that the reticulo-thalamo-cortical circuit is indicative of arousal system function in higher mammals (16). Moreover, enhanced early ERPs like MMN were associated with the dorsolateral prefrontal cortex mediated thalamic gating of sensory inputs to the auditory cortex (17). The exact reason for the circuit hyperactivity in insomnia is unclear, several neurotransmitters might be involved. First, the cholinergic neurons have been shown to be involved in regulation of sleep, in modulation of the arousal level and in the activation of the limbic system and cortical areas (18). Supersensitivity of the cholinergic neurotransmitters increases arousal level and leads to insomnia (19). Second, the 5-HT neurotransmitters facilitate but do not maintain sleep (20). The intrahypothalamic microinjection of L-5-
hydroxytryptophan decreased insomnia induced by para-chlorophenylanine in the same area (21). In addition, lower 5-HT activity in the central nervous system is the physiological substrate of high Impulsivity (22). Third, the glutamate and the gamma-amino-butyric acid (GABA) systems might contribute to the higher MMN amplitude in insomniacs. The thalamo-cortical neurons use glutamate as a neurotransmitter, which is released in the auditory cortex following sensory stimulation (23). Alcohol, which decreases glutamate neurotransmission, induces reductions in MMN (24), whereas injection of GABA receptor antagonist bicuculline increases activation of the cortical layer that generates MMN (25).

In conclusion, the higher MMN amplitude, elevated Neuroticism-anxiety, Depression and Impulsivity levels might be related to the hyperactivity of the TFC neurons in chronic primary insomnia. This might be due to weak thalamic gating mechanisms, or biochemically due to increased glutamate/cholinergic, or decreased GABAergic/5-HT neurotransmitter activities. Therefore, pursuit of balanced neuronal activities might be a therapeutic strategy for patients suffering from the disease.

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