LORETA Functional Imaging in Antipsychotic-Naive and Olanzapine-, Clozapine- and Risperidone-Treated Patients with Schizophrenia

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Key Words

Schizophrenia · Low-resolution brain electromagnetic tomography · Quantitative electroencephalography · Atypical antipsychotics · Anterior cingulum

Abstract

The aim of our study was to detect changes in the distribution of electrical brain activity in schizophrenic patients who were antipsychotic naive and those who received treatment with clozapine, olanzapine or risperidone. We included 41 subjects with schizophrenia (antipsychotic naive = 11; clozapine = 8; olanzapine = 10; risperidone = 12) and 20 healthy controls. Low-resolution brain electromagnetic tomography was computed from 19-channel electroencephalography for the frequency bands delta, theta, alpha-1, alpha-2, beta-1, beta-2 and beta-3. We compared antipsychotic-naive subjects with healthy controls and medicated patients. (1) Comparing antipsychotic-naive subjects and controls we found a general increase in the slow delta and theta frequencies over the fronto-temporo-occipital cortex, particularly in the temporolimbic structures, an increase in alpha-1 and alpha-2 in the temporal cortex and an increase in beta-1 and beta-2 in the temporo-occipital and posterior limbic structures. (2) Comparing patients who received clozapine and

those who were antipsychotic naive, we found an increase in delta and theta frequencies in the anterior cingulate and medial frontal cortex, and a decrease in alpha-1 and beta-2 in the occipital structures. (3) Comparing patients taking olanzapine with those who were antipsychotic naive, there was an increase in theta frequencies in the anterior cingulum, a decrease in alpha-1, beta-2 and beta-3 in the occipital cortex and posterior limbic structures, and a decrease in beta-3 in the frontotemporal cortex and anterior cingulum. (4) In patients taking risperidone, we found no significant changes from those who were antipsychotic naive. Our results in antipsychotic-naive patients are in agreement with existing functional findings. Changes in those taking clozapine and olanzapine versus those who were antipsychotic naive suggest a compensatory mechanism in the neurobiological substrate for schizophrenia. The lack of difference in risperidone patients versus antipsychotic-naive subjects may relate to risperidone's different pharmacodynamic mechanism.

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Introduction

Research on electrical brain activity in schizophrenic patients has developed over the last few years, particularly by means of quantitative electroencephalography (qEEG) methods. Low-resolution brain electromagnetic tomography (LORETA) represents a new approach to addressing the limited spatial resolution of EEG and, moreover, permits truly 3-dimensional tomography of electrical brain activity (current density) [1, 2]. Previous LORETA studies in unmedicated patients with schizophrenia have mainly detected an increase in slow frequencies [3–5], probably reflecting cortical hypoactivation.

Progress in the pharmacology of antipsychotics represents one of the most important successes of applied neuroscience. While antipsychotic drugs provide a basic therapeutic tool for the treatment of schizophrenia and other psychotic conditions, their effectiveness is associated with a series of unresolved questions. It is not clear, for example, which of the neurobiological mechanisms (beyond D₂ receptor blocking) is the final therapeutic target responsible for the beneficial effect on distorted information processing in schizophrenia, and for subsequent elimination or reduction of the psychotic symptoms [6].

Olanzapine and clozapine are atypical antipsychotics of the thienobenzodiazepine class. They have similarities in molecular structure and receptor profile. Both of them produce changes that can be observed on visual inspection and on quantitative analysis of EEG [7]. qEEG changes related to various atypical antipsychotic drugs have been reported in recent years [5, 8–12]. In clozapine- and olanzapine-induced qEEG changes, an increase in slow frequency bands was found, both in routinely treated patients [8, 9] and in healthy volunteers after a single dose [10, 11]. Risperidone represents the class called serotonin-dopamine antagonists. On visual evaluation of EEG, risperidone produces fewer changes than clozapine and olanzapine [7]. However, as yet there are no studies comparing the effect of atypical antipsychotics in schizophrenic patients by qEEG analysis.

To date no study focusing on the changes in the 3-dimensional distribution of electrical brain activity in patients treated with different types of atypical antipsychotics has been published. The aim of our study was to detect the changes in the distribution of electrical brain activity by the use of LORETA in patients with schizophrenia who were antipsychotic naive and those who received treatment with clozapine, olanzapine or risperidone.

With regard to previous studies, we hypothesized that antipsychotic-naïve patients will exhibit a global increase in slow frequencies, particularly in the frontal and temporolimbic structures. In medicated patients, we expected an increase in slow frequencies and to see the effect of atypical antipsychotics on regional distribution of current densities in the frontal structures.

Methods

Participants

In our study we included 41 right-handed inpatients (22 males, 19 females; median age 26.0 years, interquartile range 22.0–32.0) who were diagnosed as having schizophrenia or an acute psychotic episode (F20.0 or F23.1 according to ICD-10 classification [13]) and who were treated in the Prague Psychiatric Center. Patients experiencing their first psychotic episode who had never used any antipsychotic medication were included in the antipsychotic-naïve group. For the rest of the patients, the main inclusion criterion was that they had been receiving an antipsychotic in monotherapy. All of these patients used only one type of atypical antipsychotic and did not use any other psychotropic medication (e.g. benzodiazepines, antidepressants, anticholinergics or mood stabilizers). The minimal length of the stable monotherapy was 1 month. We divided the medicated patients into 3 groups according to the drug they used (clozapine, olanzapine and risperidone). Patients who had pathological changes in EEG patterns were excluded, as were patients who had a comorbidity (e.g. drug abuse, drug addiction, epilepsy or a history of head trauma). The data were collected over the period of 4 years between 2003 and 2006.

The control group included 20 right-handed healthy subjects (10 males, 10 females; median age 26.0 years, interquartile range 25.0–28.0). The inclusion criteria were right-handedness, a negative psychiatric family history, matching age and EEG patterns without pathological changes.

The Prague Psychiatric Center Institutional Review Board reviewed and approved this study, and a written informed consent to participate in the research was obtained from all subjects. The study was carried out in accordance with the latest version of the Declaration of Helsinki.

EEG Recording and LORETA Analysis

The 19 surface electrodes were placed according to the international 10/20 system (Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1 and O2), with all electrode impedances kept below 5 k Ω . We used the Brainscope digital amplifier system (Unimedis, Prague, Czech Republic), with Cz as a reference electrode. The EEG recording system acquired the data with a 16-bit depth and a 7.63 nV/bit resolution (i.e. approx. 130 bit/ μ V) with the dynamic range of ± 250 μ V. The data sampling rate was 250 Hz, and the acquired signals were filtered with a band-pass filter of 0.15–70 Hz after the sampling. The EEG data (30 min in duration) were recorded in a sound-attenuated room that had subdued lighting where the patients lay in a semirecumbent position, with their eyes closed but in a maximally alert state. During the recording, the alertness was controlled. If patterns of drowsiness ap-

Table 1. Demographic and clinical data

	Healthy controls (n = 20)	Antipsychotic naïve (n = 11)	Clozapine (n = 8)	Olanzapine (n = 10)	Risperidone (n = 12)	p value
Sex (male/female)	10/10	7/4	2/6	6/4	7/5	n.s. ^a
Age, years	26 (25–28)	27 (23.5–31)	26 (25.5–30.5)	24.5 (19–30)	26 (23.5–34)	n.s. ^b
Length of treatment, months	–	0	1.5 (1–15)	1 (1–2)	1.5 (1–2)	n.s. ^{b, c}
Duration of illness, months	–	2 (1–4.5)	24 (12–39)*	7.5 (2–12)	4.5 (2–5)	<0.01 ^b
Dose of the drug, mg/day	–	0	312 (231–425)	20 (15–20)	4 (4–4.2)	n.a.
CGI	–	5 (5–6)*	4 (3.75–4)	4 (3.25–4)	3.5 (3–4)	<0.001 ^b
Diagnoses (F20.0/F23.1)	–	3/8*	7/1	7/3	6/6	<0.05 ^a
Education, years	16 (15–18)	14 (12–16)	13.5 (12–17)	12 (12–16.5)	12 (11–16.5)	n.s. ^b

Data are shown as median and interquartile range. n.s. = Not significant; n.a. = not applicable; CGI = Clinical Global Impression Scale. * $p < 0.05$: significant difference after post-hoc analysis.

^a χ^2 test. ^b Kruskal-Wallis test. ^c Only medicated groups were included.

peared in the EEG, the subjects were aroused by acoustic stimulation. Before analysis of the data, artifact detection was performed visually, with the exclusion of all EEG segments containing obvious eye and head movements, muscle artifacts or a decrease in alertness. After recomputation to the average reference, spectral analysis was performed for at least 30 s of artifact-free data. The cross-spectra were averaged across the 50% overlapping windows, which yielded 7 frequency bands: delta (1.5–6 Hz), theta (6.5–8 Hz), alpha-1 (8.5–10 Hz), alpha-2 (10.5–12 Hz), beta-1 (12.5–18 Hz), beta-2 (18.5–21 Hz) and beta-3 (21.5–30 Hz) [14].

Subsequently, LORETA was used to estimate the 3-dimensional intracerebral current density distribution [1, 2]. LORETA computes the current density for 2,394 voxels in the brain as a linear, weighted sum of the scalp electrical potentials. A 3-shell spherical head model was restricted to the Talairach atlas. LORETA was restricted to the cortical gray matter and hippocampus following the Talairach probability atlas at a 7-mm spatial resolution. Since EEG spectral frequency bands are known to reflect different functions, for each subject 7 time-averaged LORETA images (in the delta, theta, alpha-1, alpha-2, beta-1, beta-2 and beta-3 frequency bands) were computed and used for further analysis [4].

Statistical Analysis

The demographic and clinical characteristics of the 4 patient groups and the group of healthy controls are reported as medians with interquartile ranges. Differences between the groups were assessed by χ^2 tests and by the Kruskal-Wallis 1-way analysis of variance test. Once a significant difference was identified using the Kruskal-Wallis test ($p < 0.05$), the Wilcoxon 2-sample ranked sum test was applied for comparing any 2 groups, with a Bonferroni correction to adjust the p values for multiple comparisons. Statistical analysis was carried out using Statistica 7.0 (Statsoft Inc.).

Statistical comparisons of LORETA-estimated current density were performed between the following groups of subjects: (1) antipsychotic-naïve patients versus healthy control subjects; (2) patients taking clozapine versus antipsychotic-naïve subjects; (3) pa-

tients taking olanzapine versus antipsychotic-naïve subjects; (4) patients taking risperidone versus antipsychotic-naïve subjects.

The localization of the differences in activity between the groups was assessed by voxel-by-voxel nonpaired t tests of the LORETA images, based on the log-transformed power of the estimated electric current density, which resulted in t statistic 3-dimensional images. In these images, cortical voxels of statistically significant differences were identified by a nonparametric approach using a randomization strategy that determined the critical probability threshold values for the actually observed statistic with corrections for multiple testing [15].

To visualize the global distributions of the t test differences, for each band we computed the location of the mean center of gravity of all voxels with positive and negative t values. To correct for multiple comparisons, a nonparametric single-threshold test was applied on the basis of the theory of randomization and on permutation tests [15]. The omnibus null hypothesis of no activation anywhere in the brain was rejected if at least 1 t value (i.e. voxel, t_{MAX}) was above the critical threshold for $p = 0.05$, determined by 5,000 randomizations [16].

Results

The patients and controls did not differ significantly in sex, age, or in their level of education. No significant difference between the patient groups was detected in the length of the treatment or in clinical evaluation (using the Clinical Global Impression scale). The length of the illness was significantly longer in the clozapine group, since clozapine is indicated in patients with schizophrenia who do not respond to previous treatment. The Clinical Global Impression scale was significantly higher in the antipsychotic-naïve group, as in these patients treatment had not yet been started. The

Table 2. Statistically significant results ($p < 0.01$) from the comparison of the antipsychotic-naive group with healthy controls

Cortical area	Brodmann area	Number of voxels					
		delta band increase		theta band increase		alpha-1 band increase	
		L	R	L	R	L	R
Anterior cingulate	10, 24, 25, 32	16	16				
Precentral gyrus	4, 6, 44	13	39				
Inferior frontal gyrus	9, 10, 11, 13, 44, 45, 46, 47	70	82		63	1	37
Medial frontal gyrus	9, 10, 11, 25	37	41				
Middle frontal gyrus	9, 10, 11, 43, 46, 47	77	89		14		13
Superior frontal gyrus	8, 9, 10, 11	54	61		2		6
Middle temporal gyrus	19, 20, 21, 22, 37, 38, 39	90	97	11	81	8	19
Inferior temporal gyrus	19, 20, 21, 37	37	39	6	30	4	4
Superior temporal gyrus	13, 21, 22, 38, 39, 41, 42	82	96	19	45	17	19
Transverse temporal gyrus	41, 42	3	3				
Insula	13	37	36		14		2
Middle occipital gyrus	18, 19, 37	26	22	19	21		
Inferior occipital gyrus	17, 18, 19	9	9	3	8		
Superior occipital gyrus	19	4	4	3	4		
Uncus	20, 28, 36, 38	21	21	21	21	3	
Fusiform gyrus, subgyral	18, 19, 20, 21, 36, 37	58	52		26	13	1
Parahippocampal gyrus	27, 28, 30, 34, 35, 36, 37	43	46	15	22		
Cuneus, precuneus	7, 17, 18, 19, 23, 31	49	49	7	5		
Lingual gyrus	17, 18, 19	16	15				
Postcentral gyrus	1, 3, 40, 43	11	35				
Posterior cingulate	30, 31	5	5				
Inferior parietal lobule	7, 39, 40	9	55				
Superior parietal lobule	7		11				
Orbital, rectal gyrus	11	18	15				
Subcallosal gyrus	13, 25, 34	8	8		3		
Angular, supramarginal gyrus	39, 40	5	18				
Extranuclear	13, 47	4	3		3		
Precentral gyrus	6, 44				9		

number of patients with the diagnosis F23.1 was significantly higher in the antipsychotic-naive group since patients experiencing their first psychotic episode were included in this group. Detailed demographic and clinical data of the study subjects, including average doses of the drugs, are shown in table 1.

Comparing antipsychotic-naive subjects and healthy controls, we found a significant current density increase in the delta, theta, alpha-1, alpha-2, beta-1 and beta-2 frequency bands. We found a global current density increase in the delta frequency band over the whole cortex, with the maximum in the right temporolimbic structures. In

the theta and alpha-1 bands we found an increase in the fronto-temporo-limbic structures. In the alpha-2 band we found a significant current density increase in the right temporal cortex and an increase of beta-1 and beta-2 current densities in temporo-occipital and posterior limbic structures. Due to the increase in current densities in large brain regions at $p < 0.05$ (which was set for this study), we used a more conservative critical threshold ($p < 0.01$, after correction for multiple testing) to demonstrate the local maxima of differences between both groups (table 2, fig. 1).

Antipsychotic-naïve group vs. controls ($p < 0.01$)

Clozapine vs. antipsychotic-naïve group ($p < 0.05$)

Olanzapine vs. antipsychotic-naïve group ($p < 0.05$)

Risperidone vs. antipsychotic-naïve group (n.s.)

Fig. 1. Images of voxel-by-voxel nonpaired t statistics of brain regional electrical activity using LORETA for selected frequency bands. The results of 4 comparisons of marked subject groups are presented. Increases of current density are shown in red, decreases are in blue. Only voxels reaching the denoted statistical sig-

nificance level are shown in color. Three orthogonal brain views in Talairach space are sliced through the region of the extreme t value, given as X, Y, Z coordinates in Talairach space and graphically indicated by black triangles on the coordinate axes. n.s. = No significant differences in the current density distribution.

Table 3. Statistically significant results ($p < 0.05$) from the comparison of patients taking clozapine with the antipsychotic-naïve group

Cortical area	Brodmann area	Number of voxels							
		delta band increase		theta band increase		alpha-1 band decrease		beta-2 band decrease	
		L	R	L	R	L	R	L	R
Anterior cingulate	24, 31, 32, 33	9	8	6	6				
Cingulate gyrus	24, 31, 32	15	17	46	46			1	
Paracentral lobule	4, 5, 6, 31			10	10				
Medial frontal gyrus	6, 8, 9	5	5	22	17				
Superior frontal gyrus	6, 8	4	6	20	18				
Fusiform gyrus, subgyral	19, 37						5		13
Parahippocampal gyrus	19, 27, 30, 35							18	30
Cuneus	17, 18, 19					4	6	15	11
Precuneus	19, 23, 24, 30, 31			3	5			7	5
Middle occipital gyrus	18, 19, 37					12	21	14	21
Inferior occipital gyrus	17, 18, 19								6
Superior occipital gyrus	19					2	4	2	4
Middle temporal gyrus	19, 21, 37, 39						23		32
Inferior temporal gyrus	18, 19, 37						12		6
Superior temporal gyrus	13, 22, 39								14
Lingual gyrus	18						1		1
Posterior cingulate	30, 31							4	1
Inferior parietal lobule	40								3
Angular, supramarginal gyrus	39						1		8

In the comparison of patients who received clozapine versus the antipsychotic-naïve group, we found a significant current density increase in the delta and theta bands in the anterior cingulate and medial frontal cortex, and a significant current density decrease in alpha-1 and beta-2 in temporo-occipital structures. All voxels that reached the critical threshold of $p < 0.05$, after correction for multiple testing, are shown in table 3.

The olanzapine group differed from the antipsychotic-naïve subjects in the theta band in the anterior cingulate and medial frontal cortex. A significant current density decrease was detected in the alpha-1, beta-2 and beta-3 bands in the occipital cortex and posterior limbic structures. A significant decrease in the beta-3 band was also observed in the anterior cingulate and frontotemporal cortex. All voxels that reached the critical threshold ($p < 0.05$, after correction for multiple testing) are shown in table 4.

Comparing the patients who received risperidone and the antipsychotic-naïve group, we found no significant differences in the current density distribution.

Discussion

In this study, we investigated the differences in the distribution of brain electrical activity in schizophrenic patients who were antipsychotic naïve and those who had received treatment with clozapine, olanzapine or risperidone.

The results of the comparison of the antipsychotic-naïve group with the healthy controls are in partial agreement with other qEEG and functional neuroimaging reports in the literature [3, 4, 17, 18]. An increase in current density in the delta and theta frequency bands in the frontal and temporolimbic-occipital cortex suggests decreased functional activity in frontal areas (hy-

Table 4. Statistically significant results ($p < 0.05$) from the comparison of patients taking olanzapine with the antipsychotic-naïve group

Cortical area	Brodmann area	Number of voxels							
		theta band increase		alpha-1 band decrease		beta-2 band decrease		beta-3 band decrease	
		L	R	L	R	L	R	L	R
Anterior cingulate	24, 31, 32, 33	2	2					12	11
Cingulate gyrus	24, 31, 32	12	10			2	2	10	9
Medial frontal gyrus	6, 8, 9, 25							10	7
Subcallosal gyrus	25, 34							3	2
Superior frontal gyrus	6, 8							2	5
Middle frontal gyrus	8							2	
Parahippocampal gyrus	19, 27, 30, 35, 36, 37					18	30	20	20
Fusiform gyrus, subgyral	19, 20, 37							11	6
Cuneus	17, 18, 19					24	17		
Precuneus	19, 23, 24, 30, 31					23	24		
Middle occipital gyrus	18, 19, 37					25	22		
Inferior occipital gyrus	17, 18, 19					9	9		
Superior occipital gyrus	19					4	4		
Middle temporal gyrus	19, 21, 37, 39			19	39	16	35		
Inferior temporal gyrus	18, 19, 37				2	3	8		
Superior temporal gyrus	13, 22, 39					2	22		1
Lingual gyrus	18					36	27	10	7
Posterior cingulate	30, 31					19	25		
Inferior parietal lobule	40					1	19		
Angular, supramarginal gyrus	39, 40						18		1

pofrontality) and global cortical hypofunction. This finding is congruent with the concept of glutamatergic dysfunction in schizophrenia, as evidenced by the reduced density of the prefrontal cortex pyramidal cell dendrites, glutamatergic synaptosomes and synaptophysine [19–21].

An increase in low band power (delta) activity has been repeatedly found in the vast majority of qEEG studies in which schizophrenic patients were compared to normal subjects. The results of a LORETA study [3] with 19 medication-free schizophrenic patients showed a general increase in delta activity over the whole cortex, particularly in the anterior cingulate gyrus and temporal lobe. Although the patients included in that study were medication free and not antipsychotic naïve, our findings are in accordance with the result. Using LORETA, Pascual-Marqui et al. [4] found an anterior excess of delta activity, an anterior-inferior deficit of theta and alpha ac-

tivity and a posterior-superior right-sided excess of beta-1, beta-2 and beta-3 frequency activity in 9 antipsychotic-naïve patients experiencing their first episode of schizophrenia. Similarly, we found a frontal increase in current density in the delta band and an increase in the beta frequency band in posterior structures. However, our results differ in the theta and alpha bands. A possible explanation may be that the changes of activity in the alpha and theta frequency bands are a little more closely related to the status of vigilance, attention and relaxation than to the psychopathology itself.

Findings in functional brain imaging studies (using positron emission tomography and single-photon emission computed tomography) in patients with schizophrenia frequently show the same regional changes as we found in the distribution of electrical brain activity, particularly in the frontal cortex (hypofrontality) and in the temporolimbic regions [17, 18].

In the comparison of the patients who received clozapine and olanzapine with the antipsychotic-naïve group, we obtained similar results: an increase in slow frequencies in the anterior cingulate and the medial frontal cortex. These results are in accordance with anatomical and functional studies in schizophrenic patients, which consistently describe volume and metabolism changes in the anterior cingulate subsequent to atypical antipsychotic treatment [8, 9, 22–24].

In another LORETA study [9] involving 25 chronically medicated patients with schizophrenia, there was an excess of delta and theta frequencies located in the right middle frontal gyrus, right inferior frontal gyrus and right insula, as well as the bilateral anterior cingulum. However, only 2 patients in this study used atypical antipsychotics, the others used conventional ones. Correlation of the clozapine-induced clinical qEEG changes with the clinical response was detected in another qEEG prospective, longitudinal study in 16 schizophrenic patients [8]. This found a significant increase in theta frequency in the electrodes over the frontocentral scalp area after 3 weeks of treatment with clozapine. These electrodes reflect activity from the frontal cortex, including the anterior cingulum.

Previous qEEG studies of antipsychotic drugs in healthy volunteers have shown a significant sedative effect compared to placebo [5, 10, 11, 25]. A study of healthy subjects [11] found an increase in electrical activity in the theta and a decrease in the alpha-2 and beta bands after a single dose of olanzapine. In another [25], there was an increase in delta power in healthy volunteers after a single dose of olanzapine, and a study in healthy men [10] found an increase in delta and theta frequencies and a decrease in alpha and beta frequencies after clozapine.

The role of the anterior cingulate cortex in the pathophysiology of schizophrenia was described in functional (positron emission tomography) [22, 23], volumetric [24, 26] and electrophysiological (LORETA) studies [27, 28]. A magnetic resonance imaging study [24] of 31 antipsychotic-naïve schizophrenics found a positive correlation between an increased anterior cingulate volume and typical antipsychotic exposure over time (2–3 years later), while increased atypical antipsychotic exposure was correlated with a decreased anterior cingulate volume. Another magnetic resonance imaging study [26] found a correlation between an increased cingulate volume and typical antipsychotic exposure. A positron emission tomography study [22] reported that clozapine, but not haloperidol, normalizes anterior cingulate regional cerebral

blood flow patterns in schizophrenia during a cognitive task. Another recent study [23] reported an increase in regional cerebral blood flow in the anterior cingulate and temporal cortex after a single dose of olanzapine in drug-free schizophrenic volunteers. Electrophysiological LORETA studies showed decreased activation in the anterior cingulate gyrus in subjects with schizophrenia [27, 28].

The absence of haloperidol or other conventional antipsychotic-treated groups represents a substantial limitation of our study. The reason for this is that to satisfy the main inclusion criterion, patients had to be receiving an antipsychotic in monotherapy, and haloperidol monotherapy treatment is no longer involved in current routine treatment standards.

In the comparison of the patients who received risperidone with the antipsychotic-naïve schizophrenia group, we found no significant changes, which may be related to its different mechanism of action. The substantial differences between clozapine and olanzapine, on the one hand, and risperidone, on the other, could be related to the mechanism of action of both classes of drug. Risperidone is characterized by a high selectivity of dopamine D₂ and serotonin 5-HT_{2A} receptors. Clozapine and olanzapine represent multiacting receptor-targeted antipsychotics, the drugs show a weak affinity to D₂ receptors and an affinity to other systems, such as the cholinergic, histaminergic, 5-HT_{1A}, 5-HT_{2C} and others [6]. Risperidone and multiacting receptor-targeted antipsychotics share antipsychotic effects but differ from each other in the induction of neuroplastic changes mediated by the brain-derived neurotrophic factor (BDNF). After administration of risperidone, reduced production of mRNA for BDNF was found in the hippocampus and the frontal and orbital cortical regions in rats. On the other hand, the chronic administration of olanzapine increased the expression of BDNF [29, 30]. Congruently, olanzapine induces volumetric changes in patients [31]. It is noteworthy that the 5-HT_{2A} antagonism itself leads to a higher production of BDNF [32, 33] and that, conversely, D₂ antagonism reduces BDNF [34]. This explains the BDNF-stimulating effect of olanzapine and clozapine. Risperidone is also a strong 5-HT_{2A} antagonist, but due to its very high affinity to D₂ receptors its D₂-mediated suppression of BDNF may prevail. Therefore, we speculate that the difference between the 2 groups of antipsychotic, in terms of the electrical brain activity detected by LORETA, would be explained by the neuroplastic effect characteristic only for the multiacting receptor-targeted antipsychotic group. These neuroplastic changes would

be responsible for the inhibitory effect on the medial frontal cortex documented by the increase of the theta and delta frequencies.

When comparing antipsychotic-naïve patients with healthy controls, we found a general increase in slow frequencies, mainly in the temporo limbic structures, which is in agreement with existing functional findings. In patients who received clozapine and olanzapine compared with those who were antipsychotic-naïve, we found the most prominent changes in the anterior cingulate and medial frontal cortex and a decrease in fast frequency activities in the occipital cortex. This could suggest a compensatory mechanism in the neurobiological substrate

for schizophrenia. The absence of any differences in the patients on risperidone compared to the antipsychotic-naïve schizophrenics may relate to its different pharmacodynamic mechanism.

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