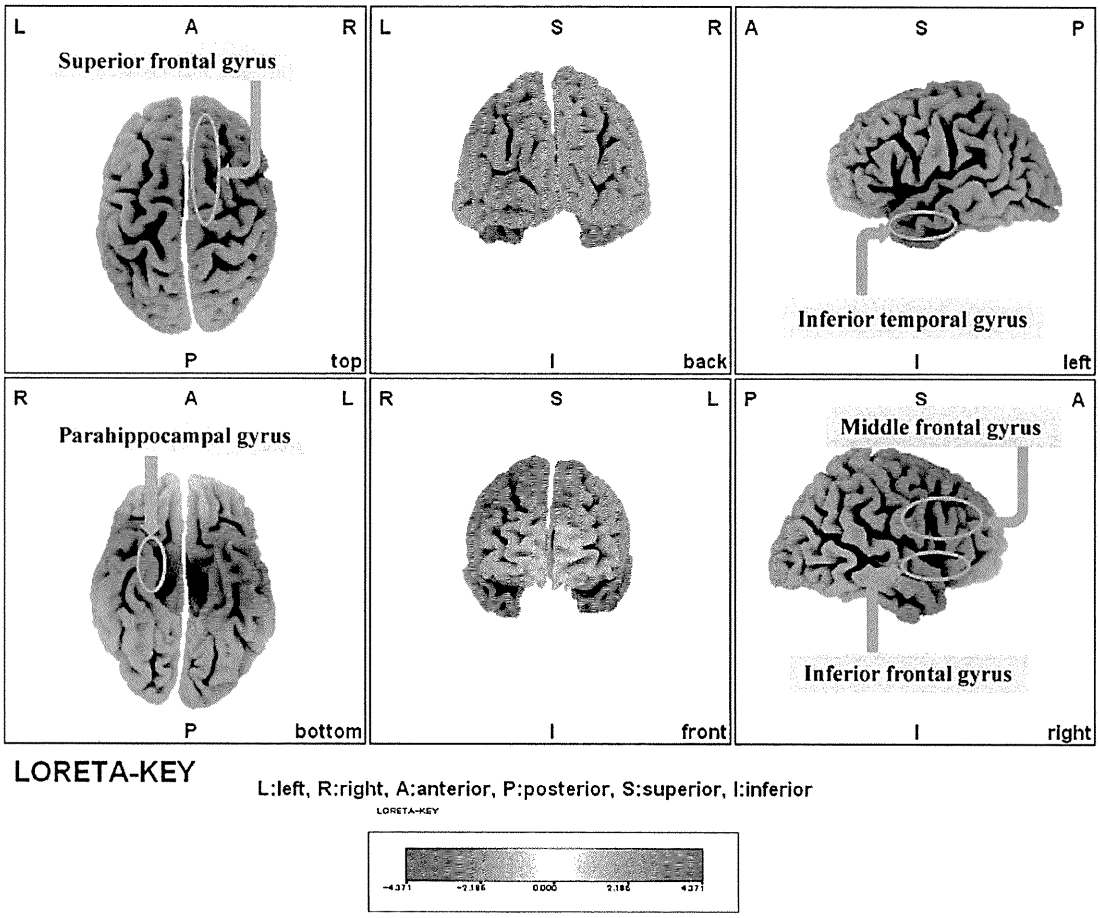

Fig. 1. Comparison of LORETA current density for delta band activity in patients with schizophrenia against normal control subjects as revealed by statistical non-parametric mapping (SnPM) voxel-wise LORETA comparisons for independent samples. Positive, zero, negative *t*-values are represented in red, white and blue, respectively. A significant increase ($P < 0.001$) in the LORETA current density for delta band activity for patients is shown in the left inferior temporal gyrus (ITG), right middle frontal gyrus (MFG), right superior frontal gyrus (SFG), right inferior frontal gyrus (IFG), and right parahippocampal gyrus (PHG).

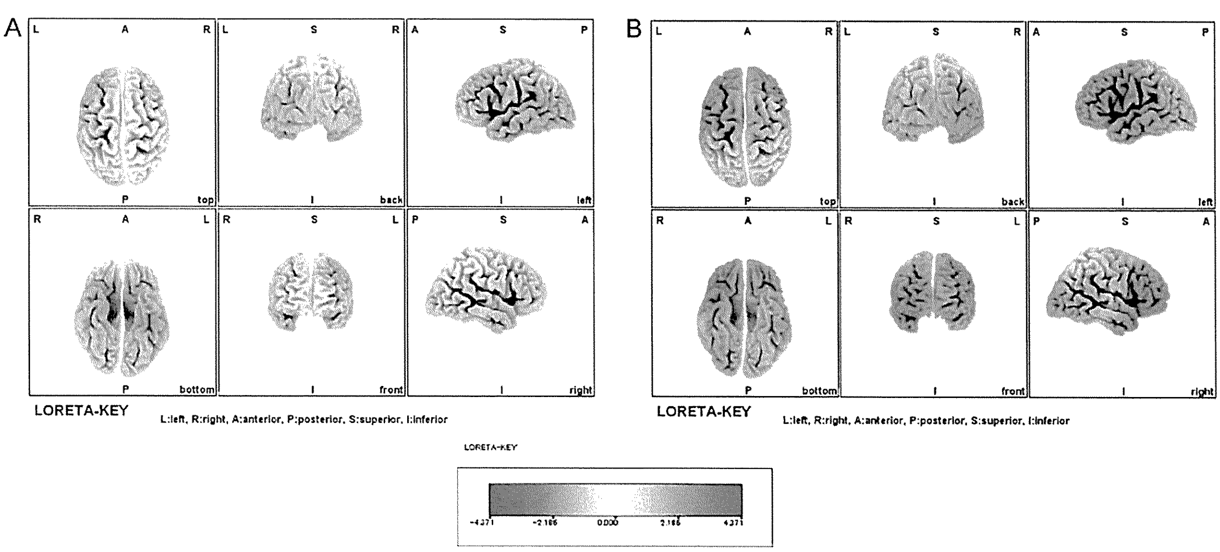

Fig. 2. Comparison of LORETA current density for theta (left) and alpha-2 (right) band activities in patients with schizophrenia against normal control subjects as revealed by statistical non-parametric mapping (SnPM) voxel-wise LORETA comparisons for independent samples. Positive, zero, negative *t*-values are represented in red, white and blue, respectively. A trend-level increase in the LORETA current density for theta (A) and alpha-2 (B) band activities is shown.

Table 2
Maximum difference of EEG activity in different frequency bands between patients with schizophrenia and healthy control subjects.

Frequency band	Extreme *t*-value	*P*-value	Extreme *t*-value: brain region predominantly involved		
			BA	Region	Right/Left
Delta (1.5–6.0 Hz)	4.37	<0.0001	20	Inferior temporal gyrus	L
Theta (6.5–8.5 Hz)	2.74	0.04	8	Middle frontal gyrus	R
Alpha-1 (8.5–10.0 Hz)	2.38	0.10	8	Superior frontal gyrus	R
Alpha-2 (10.5–12.0 Hz)	2.94	0.05	47	Inferior frontal gyrus	R
Beta-1 (12.5–18.0 Hz)	0.96	0.42	37	Parahippocampal gyrus	R
Beta-2 (18.5–21.0 Hz)	−1.75	0.19	34	Subcallosal gyrus	R
Beta-3 (21.5–30.0 Hz)	−2.06	0.06	47	Inferior temporal gyrus	R
			6	Precentral gyrus	L
			7	Precuneus	L
			7	Precuneus	L
			29	Posterior cingulate	L

Table 3
Spearman correlation coefficients between LORETA current density in discrete brain regions and SAPS and SANS Total score.

	SAPS		SANS	
	r	*P*	*r*	*P*
Right superior frontal gyrus	−0.20	n.s.	−0.54	0.02
Right middle frontal gyrus	−0.31	n.s.	−0.56	0.02
Right inferior frontal gyrus	−0.13	n.s.	−0.52	0.03
Right parahippocampal gyrus	−0.05	n.s.	−0.50	0.04
Left inferior temporal gyrus	−0.19	n.s.	−0.60	0.01

Another important finding in this study was that LORETA current density of delta activity in the left ITG was negatively correlated with severity of negative symptoms. Coutin-Churchman and Moreno (2008) reported that alcoholic patients with depressive symptoms showed significantly lower current density of delta band activity in the left temporal cortical areas, as well as medial temporal areas, including amygdala and hippocampus, compared to non-depressed patients. On the other hand, right frontopolar cortex and superior temporal cortex of depressed subjects showed increased delta activity. They also found that current densities in delta band activity at left parahippocampal cortex, left midfrontal cortex and right frontopolar cortex were negatively correlated with the Beck Depression Inventory (BDI) score. A negative correlation between delta power in the frontal areas and the BDI score was also reported in a magnetoencephalographic study (Wienbruch et al., 2003). These latter findings are in line with the results reported here (Table 2), showing an association between enhanced delta band activity and severity of negative symptoms, including affective disturbances.

Tislerova et al. (2008) reported that clozapine enhances LORETA current source density for delta and theta bands activity in the anterior cingulate cortex and medial frontal cortex in neuroleptic-naïve patients with schizophrenia. Another study (Gross et al., 2004) reports that the greater improvement in negative symptoms by treatment with clozapine was associated with the larger increase in 3.5–7.0 Hz power band activity in fronto-central areas. Together with the link between the increased delta band activity in prefrontal cortex and fewer negative symptoms (Table 2), the results of these previous studies suggest that an increase in slow activity in specific brain regions may represent a compensatory mechanism against the pathological process intrinsic to schizophrenia.

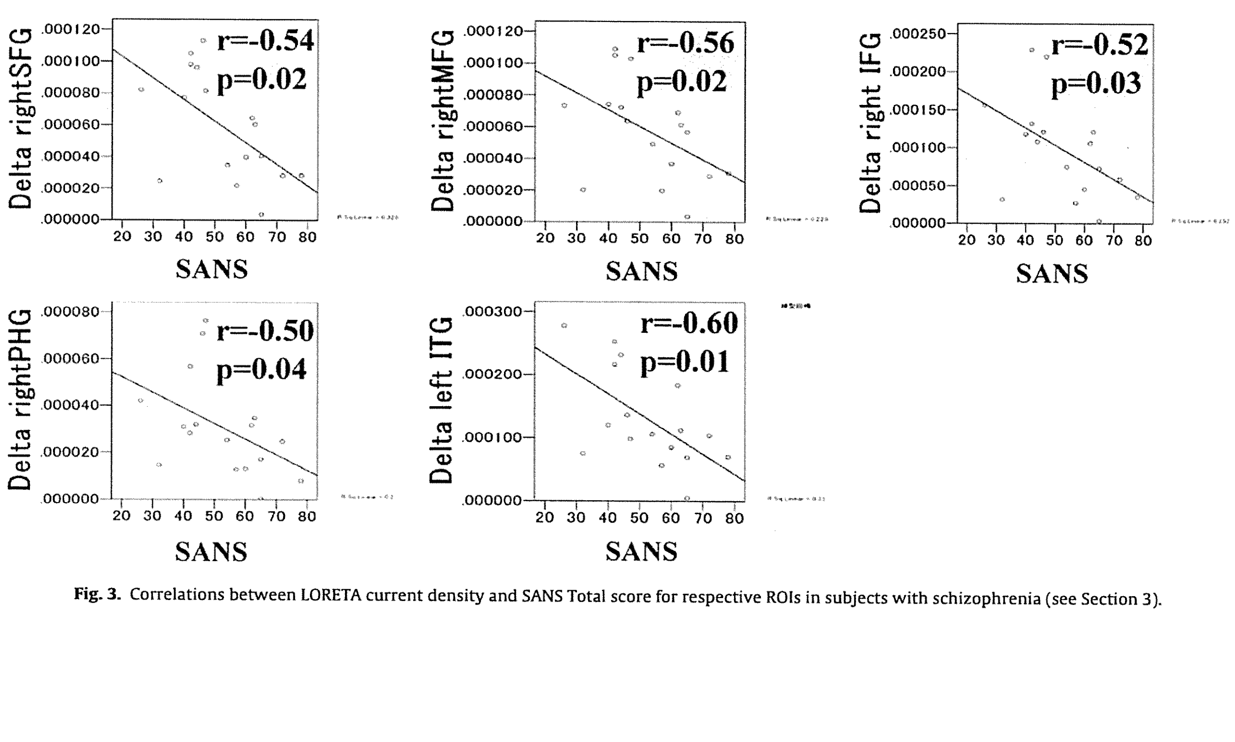

Fig. 3. Correlations between LORETA current density and SANS Total score for respective ROIs in subjects with schizophrenia (see Section 3).

Dang-Vu et al. (2008) found transient changes in brain activity to be consistently associated with slow wave (>140 μV) and delta wave (75–140 μV) during slow wave sleep (SWS) in 14 healthy control subjects. Significant increases in activity were related to these waves in several cortical areas, including the inferior temporal, medial prefrontal, precuneus, and posterior cingulate areas. Compared with baseline activity, slow waves were associated with significant activity in the parahippocampal gyrus, cerebellum, and brainstem, whereas delta waves were related to frontal responses (Dang-Vu et al., 2008). They concluded that SWS is not a state of brain quiescence, but rather is an active state during which brain activity is consistently synchronized to the slow oscillation in specific cerebral regions (Dang-Vu et al., 2008). Their results are in line with our contention that slow waves, such as delta band activity, may be an "active condition" which is likely to compensate for the pathological conditions in schizophrenia.

Harmony et al. (1996) argued that an increase in delta EEG activity during mental tasks may be related to subjects' attention to internal processing. Therefore, an increase of delta band activity might be related to a mechanism of reducing external input, that is, subjects who are capable of reducing inputs might also be able to cope better with psychosis, and have less secondary negative symptoms. We also found a trend-level increase in theta and alpha-2 band activities in patients with schizophrenia. Previous QEEG studies report an increase in theta activity in subjects with schizophrenia. For example, Veiga et al. (2003) observed that patients with chronic schizophrenia show increased delta and theta frequency bands activity in brain areas, such as the right middle frontal gyrus, right inferior temporal gyrus, and right insula, as well as bilateral anterior cingulate gyrus, using LORETA. These previous data from chronic patients and the present results from first-episode patients indicate that increased slow activity in frontal regions is independent of the clinical stage, and thus, intrinsic to schizophrenia.

Some studies report an increase in the alpha power over the frontal regions in schizophrenia (Nakagawa et al., 1991; Kahn et al., 1993). A recent analysis of the current density distribution also showed "anteriorization" of alpha activity in first-episode schizophrenia (Begre et al., 2003), which is in partial agreement with the current data showing a trend-level increase in alpha-2 band activity in the patients (Table 2, Fig. 2).

A major limitation in our study is the relatively small number of subjects. This might have confounded some of the present results, e.g. correlations between delta band activities vs. negative symptoms.

5. Conclusion

In conclusion, LORETA analysis of three-dimensional distribution of EEG current density suggest aberrant electrophysiological activity in some brain regions, e.g. prefrontal cortex, is associated with negative symptoms. Increased delta band activity, related to fewer negative symptoms, may represent a response to the pathological process intrinsic to schizophrenia.

Acknowledgements

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Chapter 7
Electrophysiological Imaging Evaluation of Schizophrenia and Treatment Response

Tomiki Sumiyoshi, Yuko Higuchi, Toru Ito, and Yasuhiro Kawasaki

Abstract Neuroimaging data provide various insights into altered functions and structures in the brain of subjects with schizophrenia. While some blood flow measures, e.g. functional magnetic resonance imaging and positron emission tomography, are characterized by high spatial resolutions, their time resolutions are in the range of second order. In contrast, electromagnetic recordings, e.g. electroencephalography (EEG) and magnetoencephalography, directly detect neural activity that occurs in the range of milli-second order. In spite of its feasibility, analysis with traditional EEG methods has been associated with the limited ability to localize aberrant signals. However, the recent development of imaging technique, such as low resolution electromagnetic tomography (LORETA) and its modified versions (e.g. sLORETA), improves the spatial resolution of EEG at rest and event-related potentials (ERPs), such as P300 and mismatch negativity by providing three-dimensional distribution pattern of these electrophysiological activities. In this chapter, the authors present recent findings from electrical neuroimaging studies of schizophrenia in relation to the neural basis of psychotic symptoms and cognitive deficits of the illness, as well as treatment response. These research areas are likely to facilitate the development of practical and reliable biomarkers to predict symptom severity, improve long-term outcome, and pave a new avenue to early intervention of schizophrenia.

Keywords EEG · Event-related potentials · P300 · MMN · Neuro imaging · LORETA · Cognition · Schizophrenia

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Abbreviations

AAPDs	Atypical antipsychotic drugs
EEG	Electroencephalography
LORETA	Low resolution electromagnetic tomography
MMN	Mismatch negativity

Introduction

There is considerable evidence for associations between social functioning/community outcome and cognitive function, as evaluated by neuropsychological tests, such as the MATRICS Consensus Cognitive Battery in patients with schizophrenia [1]. Therefore, neural substrates underlying impaired cognitive performance need to be elucidated, particularly for the development of novel therapeutic methods for the illness.

While brain imaging methods based on blood flow, e.g. functional magnetic resonance imaging and positron emission tomography, are characterized by high spatial resolutions, their time resolutions are limited compared to neurophysiological paradigms, e.g. electroencephalography (EEG) and magnetoencephalography. Specifically, electrophysiological biomarkers, such as EEG and event-related potentials (ERPs), have been suggested to provide objective indices of cognitive dysfunction in schizophrenia, and be more sensitive to drug-induced changes compared with other functional imaging modalities [2].

Recent development of imaging technique, such as low resolution electromagnetic tomography (LORETA) [3] and its modified versions (e.g. sLORETA) [4], has improved the spatial resolution of ERPs, e.g. P300 and mismatch negativity (MMN), by providing three-dimensional distribution pattern of these electrophysiological activities. This chapter provides recent findings from electrical neuroimaging studies on neural basis for psychopathology of schizophrenia as demonstrated by current source imaging of EEG and ERPs in discrete brain areas, and response to psychotropic drugs in relation to cognition and functional outcome.

LORETA Imaging of EEG in Schizophrenia

Scalp distributions of EEG power of various frequency bands are generally ambiguous [5], and depend on the reference sites used. Therefore, numerical analyses, such as dipole source modeling, are required to obtain precise locations of EEG generators.

LORETA has been developed to provide three-dimensional tomography of brain electrical activity, which only requires simple constraints ("smoothness of the solution"), and predetermined knowledge about the putative number of discernible source regions is not necessary (Fig. 7.1). With this method, brain electrical data

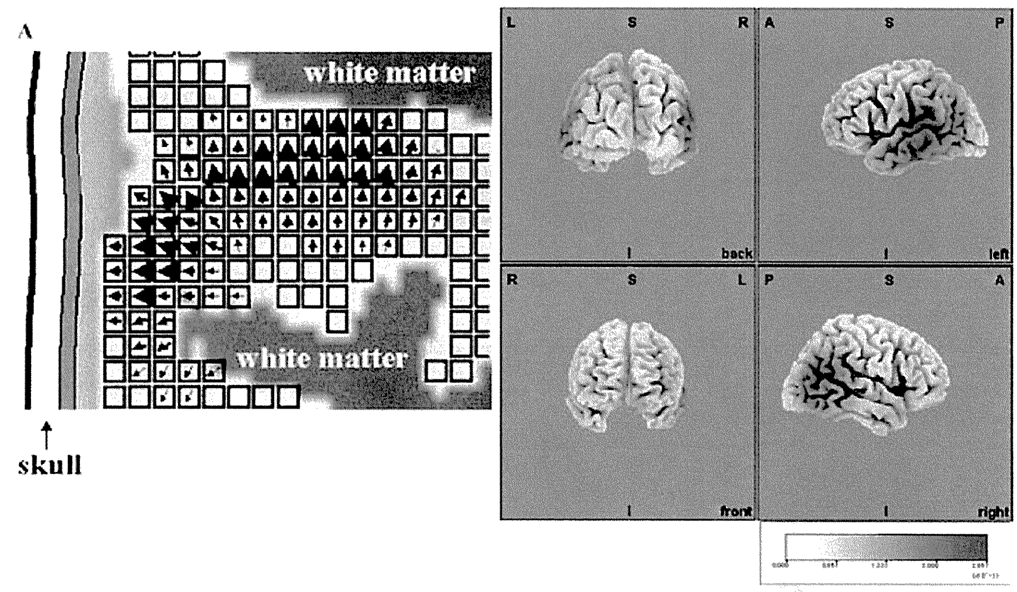

Fig. 7.1 Concept of low resolution electromagnetic tomography (LORETA) developed by Pascual-Marqui [3]. Three-dimensional imaging of LORETA values [mA/mm^2] is derived from 2394 voxels of the whole brain [8]

with high time resolution are transformed into functional imaging of brain activities, since brain electrical activity can be analyzed separately for the different EEG frequency ranges. LORETA has also been widely used for statistical comparisons of intracranial current density distributions between control subjects and patients with neuropsychiatric disorders [6, 7].

Previous investigations [3, 8] suggest that enhanced delta band activity in the prefrontal cortex is associated with the pathophysiology of schizophrenia. Specifically, negative symptoms have been associated with structural impairment in the prefrontal cortex, and have been hypothesized to arise from decreased dopaminergic activity in this brain region [9]. These observations indicate a role for prefrontal cortex in the generation of negative symptoms. With these backgrounds, we sought to determine if some components of EEG, such as delta band activity, would be increased in brain areas relevant to the pathophysiology of schizophrenia, e.g. prefrontal cortex.

As shown in Fig. 7.2 comparisons of current source density, as represented by LORETA values, between patients with schizophrenia and healthy control subjects revealed a significant increase in delta band activity for patients, with a maximum difference found at the left inferior temporal gyrus. A significant increase in delta band activities was also found for the right middle frontal gyrus, right inferior frontal gyrus, right superior frontal gyrus, and right parahippocampal gyrus. These data suggest LORETA analysis of three-dimensional distribution of EEG current density provides a measure of aberrant electrophysiological activity specific to the brain regions responsible for the manifestation of negative symptoms.

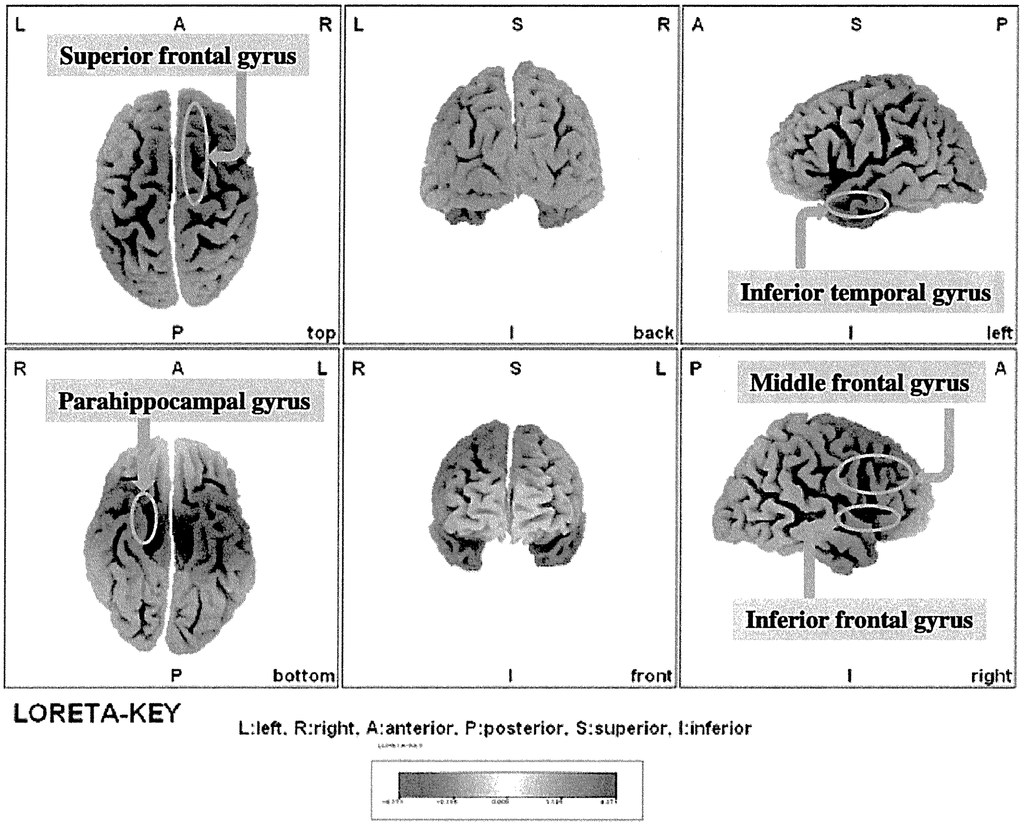

Fig. 7.2 LORETA current source density of *delta* band activity is increased in schizophrenia ($P < 0.001$, Bonferoni correction)

P300 Current Source Imaging and Psychopathology

Reduced amplitude of the P300 component during the auditory oddball task is one of the most consistent findings in patients with schizophrenia [10–12] (Fig. 7.3). However, little information is available about exact relationship between the clinical symptomatology of schizophrenia and the neurophysiological disturbances underlying the P300 abnormality. It is reasonable to assume that anatomically distinct neural substrates responsible for positive or negative symptoms independently contribute to the generation of the P300 component, because this ERP measure is thought to be a composite representation of neural activity in anatomically distinct generators [13–16].

To test this hypothesis, LORETA was used to compute the voxel-wise distribution of brain electrophysiological activity of the P300 component in order to identify brain regions in which the P300 current density is correlated with severity of psychotic symptoms of schizophrenia. Then, we applied the statistical parametric mapping (SPM) methods [17] to LORETA current density images of the P300 component [18, 19].

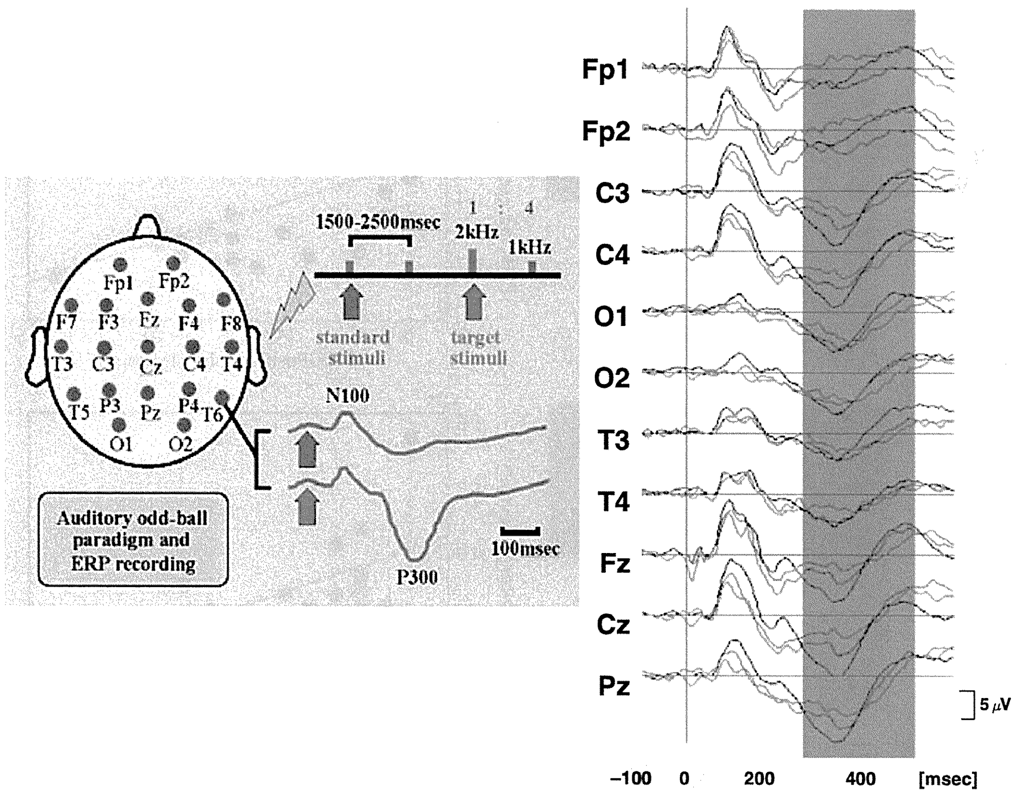

Fig. 7.3 Impaired P300, an event-related potential (ERP), as an endophenotypic marker of schizophrenia. In the right figure, black lines represent data for normal controls, while blue and red lines indicate data for patients before and after treatment with olanzapine, respectively

Results of the SPM one-sample t-test showed that P300 sources are localized in the bilateral medial frontal and medial parietal cortex, bilateral superior temporal gyrus (STG), right temporo-parietal junction, and left lateral prefrontal cortex. With regard to the relationship between the P300 current density and the BPRS Total score, voxel-based whole brain analysis without any hypothesis identified peak voxels of significant negative correlation located at the left STG and right medial frontal region. As shown in Fig. 7.4 (*left*), statistically significant voxels formed clusters within these brain regions. Mean current density values of the cluster in the STG elicited significant relationships with the Positive subscale score Fig. 7.4 (*right*). On the other hand, current density values of the cluster in the medial frontal region revealed a significant relationship with the Negative subscale score.

These findings indicate pathological neural activities of anatomically distinct generators contribute to the generation of the abnormal P300 component [20]. Our data were consistent with the proposal that negative symptoms are associated with neural deficits in the frontal lobe, while those in the temporal lobe are responsible for positive symptoms [21–23]. Taken together, the present results support the concept that the abnormal functional connectivity of fronto-temporal neural network plays a crucial role in the pathophysiology of schizophrenia [24–27].

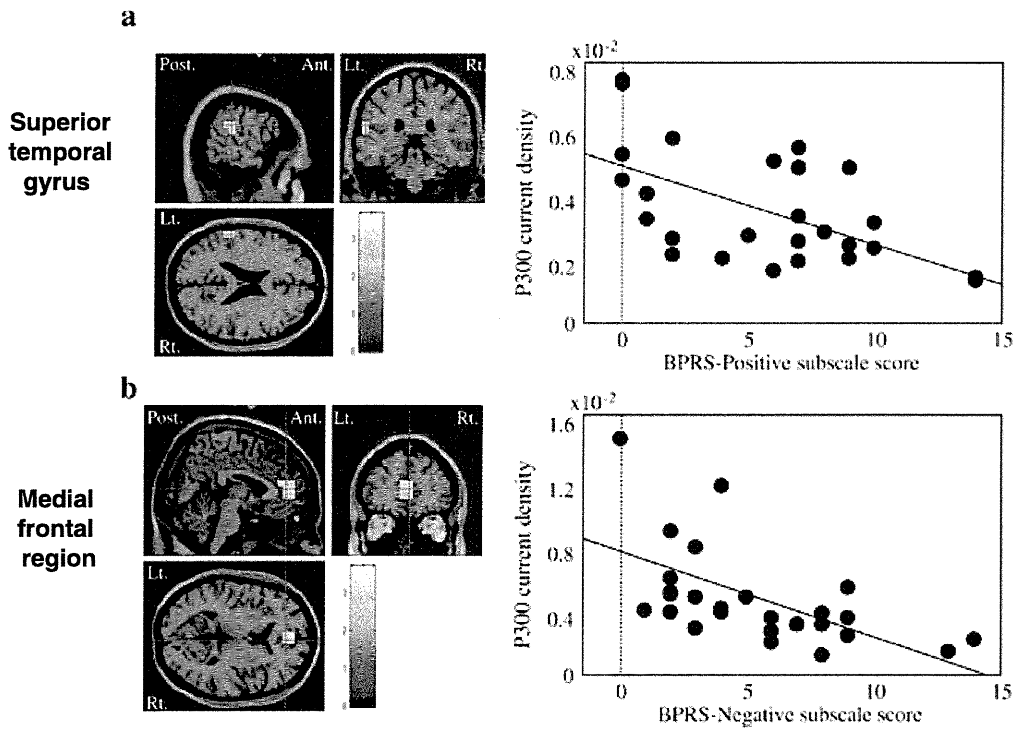

Fig. 7.4 Severity of psychotic symptoms is correlated with P300 current source density in discrete brain regions: A LORETA study [20]

ERPs Activity in Discrete Brain Regions and Effect of Neuroleptic Treatment

P300 amplitudes have been reported to be diminished in patients with schizophrenia, which differs in its effect size topography across the midline and temporal electrode sites [11, 28]. Specifically, Kawasaki et al. [29] found negative correlations between auditory P300 amplitudes and severity of psychotic symptoms of schizophrenia. Renoult et al. [30] report a positive correlation between differences in P300 amplitudes at temporal sites (T4-T3) and severity of positive symptoms and worse global functioning, consistent with the association between low P300 amplitudes and verbal memory deficits in schizophrenia [31, 32]. We reported the first observation that P300 current source density, as evaluated by LORETA, is decreased in several brain regions, especially the STG, precentral gyrus, middle frontal gyrus, and presumes (all in the left side) in patients with schizophrenia as compared with normal controls (Fig. 7.5) [33]. Our findings have been confirmed by an independent group of investigators [34].

Cognitive function, such as verbal memory, attention, and executive function, is a major determinant of outcome in patients with schizophrenia [35, 36]. The second generation antipsychotics, or so-called "atypical antipsychotic drugs (AAPDs)", have been found to partially improve cognitive disturbances of schizophrenia [37]. There is accumulated evidence for the ability of AAPDs, e.g. clozapine, olanzapine, risperidone, quetiapine, melperone, and ziprasidone and perospirone to ameliorate

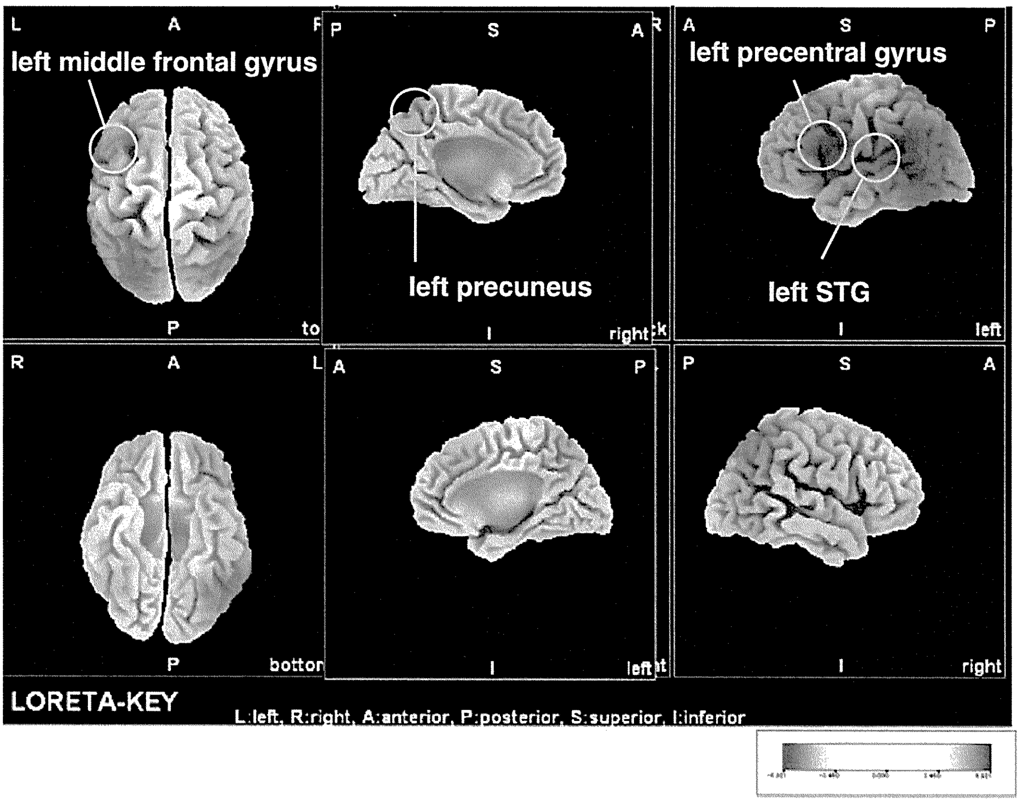

Fig. 7.5 Statistical non-parametric mapping on LORETA images of P300 current density. LORETA values in the marked areas in the left hemisphere were lower for schizophrenia patients compared to control subjects ($P < 0.001$) [33]

cognitive impairments in patients with schizophrenia (reviewed by Sumiyoshi et al. [38]), although their effects have been under scrutiny [39–41]. So far, there is limited information about the neurophysiological mechanisms underlying the ability of neuroleptic treatment to modulate cognitive performance in subjects with schizophrenia.

Umbricht et al. [42] found that treatment with clozapine but not haloperidol increased P300 amplitudes in patients with schizophrenia. Subsequently, Niznikiewicz et al. [43] observed an increase in P300 amplitudes in left temporal electrodes during treatment with clozapine, indicating a region-specific response to pharmacological treatment. We conducted clinical trials [33, 44] to determine if decreased P300 current source density in brain regions responsible for the generation of psychopathology, such as the left STG and prefrontal cortex, is recovered by long-term treatment with olanzapine, and if this change in P300 activity is correlated with improvement of cognitive performance and functional outcome in patients with schizophrenia.

As shown in Fig. 7.6 LORETA images of P300 from patients at baseline elicit lower P300 current density in the left hemisphere compared with normal controls. However, after 6-months treatment with olanzapine, P300 current density in the STG was increased, and the left-dominant laterality pattern of P300 current source

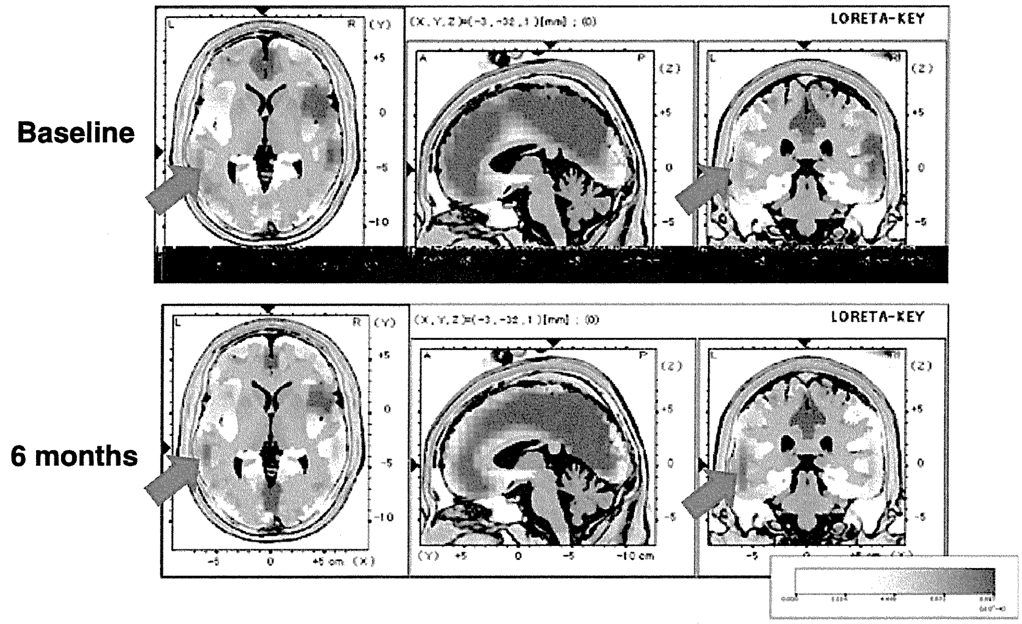

Fig. 7.6 LORETA images of P300; effect of olanzapine treatment. Six-month treatment with olanzapine enhanced P300 current source density in the left STG (indicated by *arrows*) [33]

density was noted, which is similar to the pattern of healthy controls [33, 44]. Moreover, significant correlations were noted between changes of verbal memory performance and LORETA values of the left STG, and between changes of quality of life and LORETA values of the left middle frontal gyrus (Fig. 7.7) [33]. These observations suggest that changes in cortical activity, as measured by EEG, are

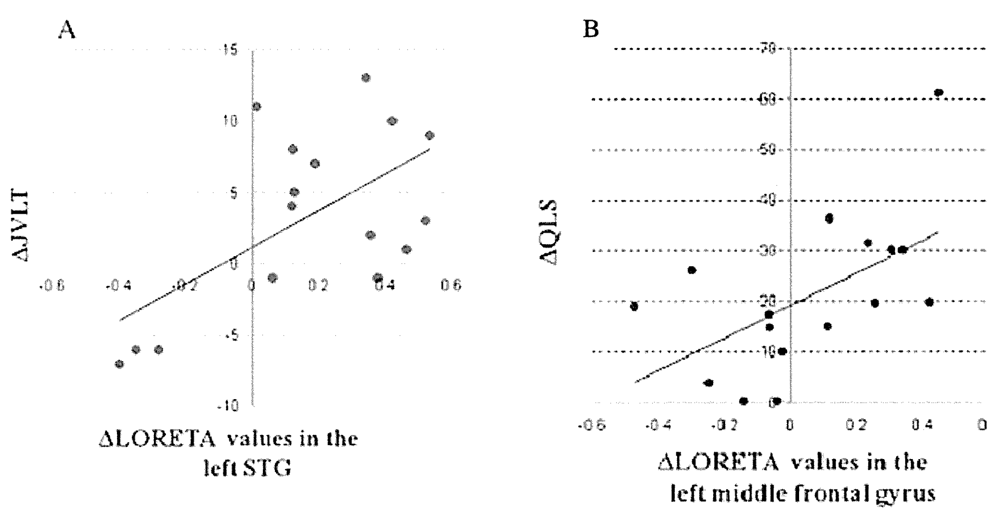

Fig. 7.7 (**A**) Changes in P300 current source density in the left STG by olanzapine were correlated with improvement in verbal memory, as measured by the Japanese Verbal learning Test (JVLT). (**B**) Changes in P300 current source density in the left middle frontal gyrus by olanzapine were correlated with improvement in quality of life, as measured by the Quality of Life Scale (QLS)

responsible for the ability of some antipsychotic drugs to improve cognitive and functional status in patients with schizophrenia.

From the clinical point of view, it is meaningful to examine the effect of type of antipsychotic drugs on the pattern of ERPs activation, as these compounds have been reported to possess differential profiles in terms of binding affinity for various neurotransmitter receptors [45]. Specifically, postmortem studies report that the serotonin-5-HT1A receptor density is increased in prefrontal cortical areas in subjects with schizophrenia [46, 47], suggesting altered 5-HT1A receptor-mediated transmission in this brain region [48, 49]. This concept is in agreement with clinical observations that augmentation therapy with 5-HT1A partial agonists, e.g. buspirone and tandospirone, enhanced the performance on some neuropsychological tests representing frontal lobe function in patients with schizophrenia [38, 50]. Therefore, it is conceivable that neural activity in frontal cortical regions would be enhanced by treatment with antipsychotic drugs with agonist actions at 5-HT1A receptors, such as perospirone [45], in patients with schizophrenia.

Using the same treatment paradigm as in the olanzapine study, above, we investigated the effect of perospirone on P300 current source density, as evaluated by the sLORETA method [4], in patients with schizophrenia, and examine the relationship between changes of P300 activity vs. performance on a cognitive task measuring the ability to evaluate component actions of social situations, which is related to frontal lobe function. As shown in Fig. 7.8 comparison of P300 current source density between baseline and 6-month after the start of treatment revealed a significantly enhanced neural activity in the left superior frontal gyrus, while conventional assessment of P300 amplitudes and latency were not significantly changed [51]. Some of the subjects studied here had been pre-treated with other antipsychotic drugs, including olanzapine, which are devoid of a noticeable affinity for 5-HT1A receptors. Therefore, our observations with perospirone provide further support to the

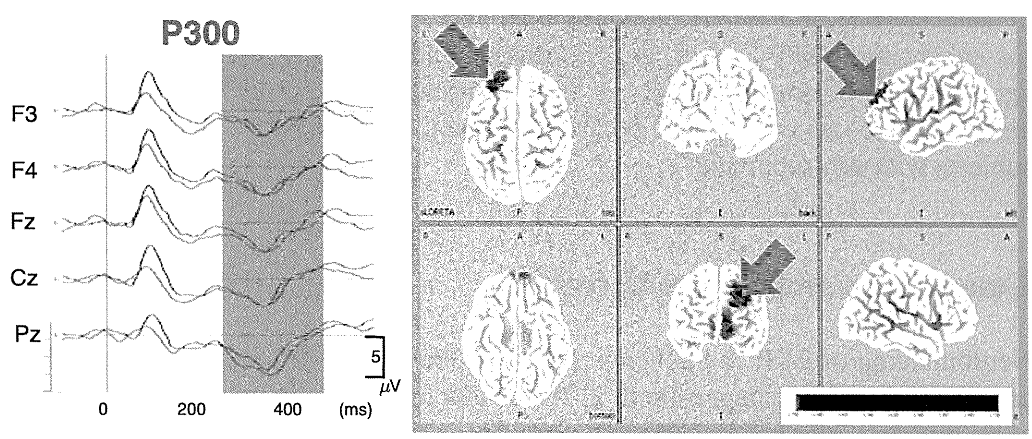

Fig. 7.8 Effect of perospirone on P300 current source density in patients with schizophrenia. Six-month treatment with perospirone enhanced P300 activity in the left superior frontal gyrus (comparison of P300 sLORETA values between before and after 6-month treatment) [51]

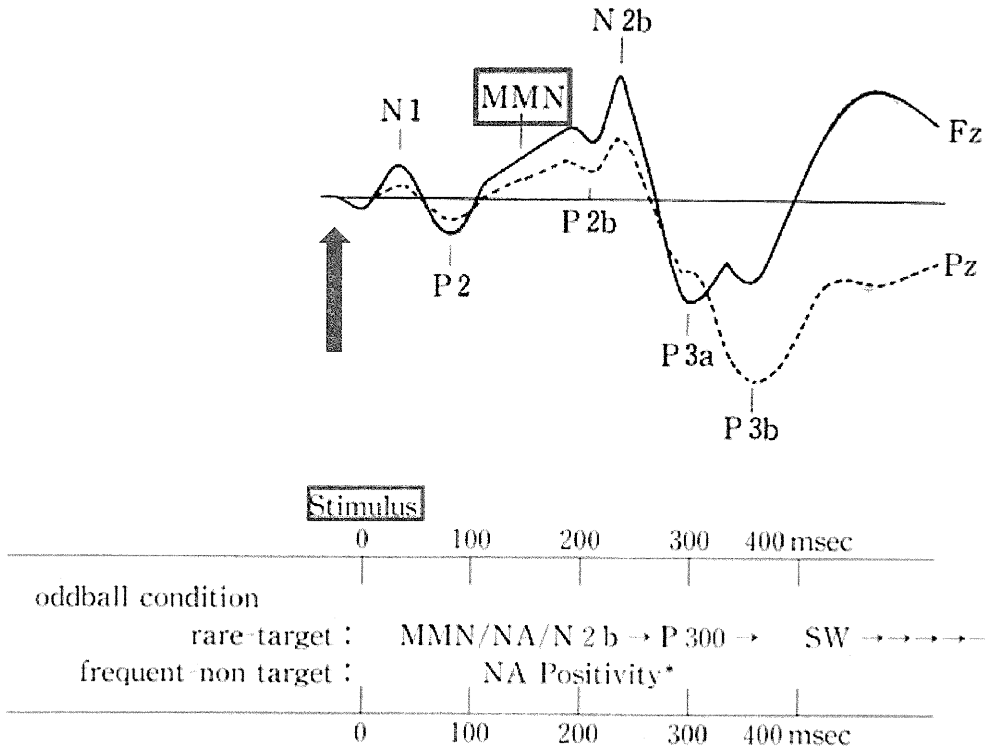

Fig. 7.9 ERP waveforms in response to the odd-ball tasks (rare-target)

concept that stimulation of 5-HT1A receptors may mediate the ability of this agent to increase P300 current source density in the left prefrontal cortex.

Mismatch negativity (MMN) is another component of ERPs generated in response to occasional variations of acoustic stimuli (Fig. 7.9) and is suggested to reflect *pre-attentive* cognitive operations [52]. We recently found the addition of tandospirone, a 5-HT1A partial agonist and anxiolytic [50, 53], was effective for enhancing MMN [54]. This is consistent with previous reports that 5-HT1A agonists, e.g., tandospirone [50, 53, 55], buspirone [38], and perospirone [51, 56], ameliorated cognitive deficits related to frontal and temporal lobe function in subjects with schizophrenia.

Conclusions and Future Directions

Neuroimaging of ERP components, such as P300 and MMN, are also expected to provide an objective diagnostic tool. We conducted discriminant function analysis of multivariate linear model using the statistical parametric mapping (SPM) in order to construct an optimal model to distinguish between healthy controls and patients with chronic schizophrenia [57] (Fig. 7.10). Although the classification power was not enough due, possibly, to the fact that these patients were mixed in terms of

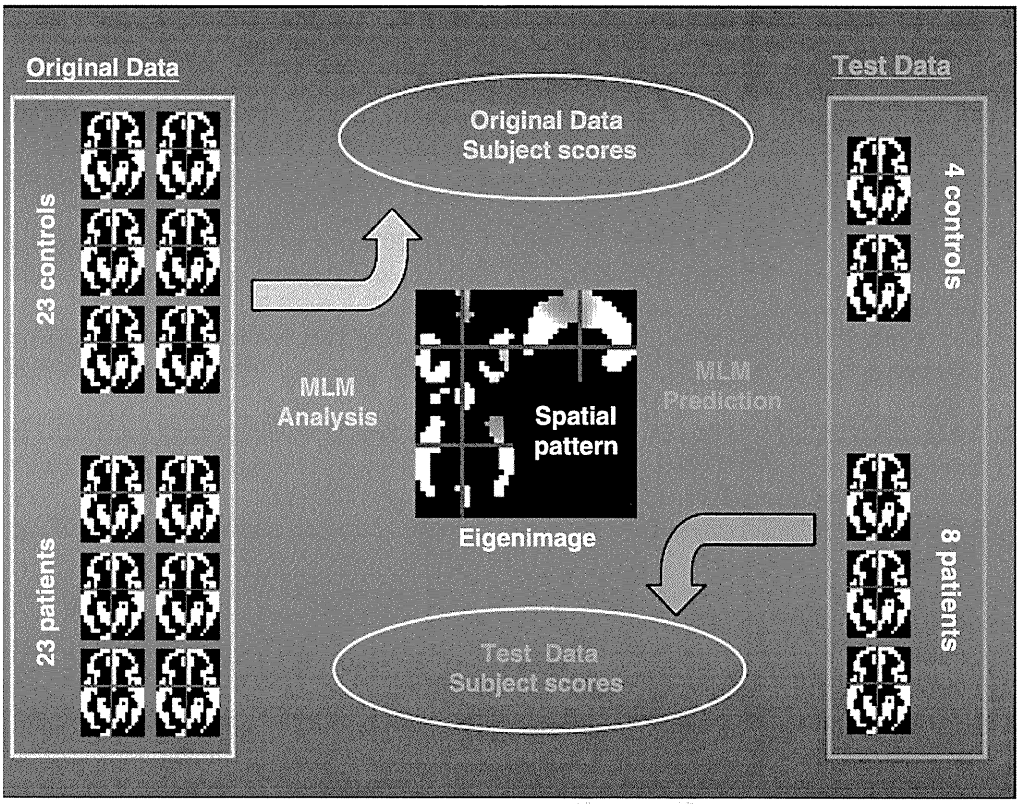

Fig. 7.10 The general scheme of discriminant function analysis of multivariate linear model (MLM) *using the* statistical parametric mapping [57]

treatment status [57], application of this method to drug-naïve subjects with first episode schizophrenia and those at the prodromal stage is likely to facilitate early intervention into the illness.

In conclusion, the utilization of neuroimaging methods enhances spatial resolution of electrophysiological evaluation, e.g. ERPs, which would provide feasible and reliable biomarkers, objective assessments of psychosis and cognition, and predictive measures of treatment response, and facilitate early diagnosis and intervention of schizophrenia.

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〔特集：認知機能障害に対する治療をどう評価するか〕

統合失調症の認知機能障害に対する認知矯正療法の効果*

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要約：統合失調症の認知機能障害を改善するリハビリテーション手法である認知矯正療法には多様な種類がある．統合失調症では認知機能障害をもつ人が8割と多く，機能的転帰に与える影響が広範囲にわたるといわれている．薬物療法による認知機能障害の改善は限定的であることから，認知矯正療法のような心理社会的手法の役割が注目されている．認知矯正療法の最終的な目的は機能的転帰の改善であることから，精神科領域での興味は増し，多数の効果研究やメタ分析が発表されている．本稿では認知矯正療法の異なる側面や，効果の評価ポイント，効果指標の例などについて解説する．全ての認知矯正療法が認知機能の改善を目的としている点は共通しているが，特定の認知機能を標的としているか否か，認知機能の改善を補償的あるいは回復的にとらえるのかなどで異なる．異なる手法の中で効果が示されているものからIPT，NEAR，CET，NETの4つを抜粋し，それぞれの特徴を紹介する．認知矯正療法には，認知機能を訓練するセッションに加えて，般化を目的としたセッションが組み込まれていることが多いが，その手法は言語セッションや就労訓練など多様である．同様に，認知矯正療法は単独で実施するのではなく，デイケアのような精神科リハビリテーションの一部として実施するのが最も効果的だと考えられている．またコンピューターを用いる場合でも，臨床スタッフの役割が重要である．認知矯正療法の効果を評価する際には，効果指標，対照条件が異なる場合が多いため，留意する必要がある．また効果研究では効果サイズが報告されているため，効果の大きさの違いにも注意し，異なる手法の効果を吟味することが求められる．

キーワード：統合失調症，認知機能障害，リハビリテーション，心理社会的手法，機能的転帰

I. 統合失調症の認知機能障害とは

認知矯正療法の目的は認知機能障害を改善し社会機能（機能的転帰）を改善することである．認知機能障害は前駆期から認められ，急性期に悪化するが安定期には顕著な改善はしない．統合失調症のおよそ8割に認知機能障害が認められ，神経心理検査の結果では健常者の平均と比較して1.5標準偏差ほど低い．認知機能障害と機能的転帰との関連は，Greenらの論文で示されており（Green et al, 2000），なかでも言語記憶，作業記憶，遂行機能，覚度は，心理社会機能，自立生活機能，就労機能に密接に関連しており，予後改善につながる重要な治療標的である．

II. 認知矯正療法とは

認知矯正療法は精神疾患のリハビリテーション手法の一種としてとらえることができる．認知矯正療法には種類があり，主たる分類として訓練手法により，反復練習による基礎的認知機能の強化，課題戦略訓練を重んじるものの2種類に分けられる．反復練習では処理速度や注意などの基礎的認知機能を，段階的に難易度が高くなる課題を用いて繰り返し訓練し，強化し，基盤となる情報処理システムを強化することを目的とする．課題戦略訓練では，課題への取り組み方法を工夫することを訓練し，基礎的認知機能の低下による障害に対する補償的なアプローチを習得し，訓練内容を日常生活場面に応用することを目的としている（Kurtz and Sartory, 2010）．ただ実際の臨床場面における実践では，反復練習と課題戦略訓練の両方を行う場合が多い．

反復練習を用いた初期の手法にはWagner（1968）によるもの，課題戦略訓練にはMeichenbaum and Cameron（1973）によるものが代表的であり，それぞれ介入群では統制群に比較して認知機能の改善が報告されている．認知矯正療法の発展にともない，パッケージ化された手法の種類が増え，効果研究やメタ分析の結果も盛んに報告され，海外では精神科リハビリテーションにおける一般的な治療メニューとして普及しつつある．

認知矯正療法は薬物療法と組み合わせて導入され，認知機能障害の改善に一定の効果を示している．認知矯正療法は病態水準や病相期の異なる患者を対象として，デイケアなどの包括的な治療プログラム内で実施されることが一般的である．これは，認知矯正療法で改善した認知機能を，

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デイケアの治療プログラム内や生活場面で実践し，般化が促進されるためである．

III. 異なる手法について

認知矯正療法には種類があり，認知機能障害の改善を目的とする点は共通しているが，対象とする障害領域や手法の違いにより特徴付けられる（表）．記憶や問題解決など特定の神経認知を標的とする手法に対して神経認知全般を対象にする手法がある．特定の神経認知を標的とした手法の効果研究において，標的とした領域の改善と，それ以外の領域において見られた改善には有意な差がなかったとする報告がある（Medalia and Choi, 2009）．

認知機能障害をどのようにとらえるかという理論的な立場の違いにより，損なわれた機能（例：記憶）を残存する機能（例：推論）で補う補償的手法と，障害のある機能の回復を目指すという手法がある．補償的手法では課題戦略の訓練を用いるのに対し，回復を目指す手法では，反復練習に重点がおかれる．上述したように，実際の臨床場面ではいずれかに限定するのではなく，補償的アプローチと回復的アプローチの両方をとることが多いようである．

認知矯正療法では，コンピューターを使用する手法と紙と鉛筆で課題を行う手法がある．コンピューターを使用する手法は増えつつあり，複数の利点があるためと思われる．例として，多様な強化子の提示が可能である，視覚や聴覚など複数の知覚に訴える刺激や教示の提示，反復練習を無制限に実施できる，患者の水準に適した難易度設定，標準化された課題内容，正確で迅速なフィードバックなどがあげられる（Grynszpan et al, 2011）．対人交流を苦手とする患者にとっては，コンピューターを介した形式自体が導入に役立つであろう．認知矯正療法でコンピューターを用いる場合，一度に複数の患者が治療を受けることが可能であり，対価格効果の点から魅力的である．その一方で，コンピューターも紙や鉛筆と同様に，治療を行う媒体でしかないため，治療者の訓練や技量が一定の水準を満たしていることは必要である．

認知機能障害を改善するための治療に付随して，改善を般化するために用いられる手法には，言語セッション，就労訓練，SST（Social Skills Training または社会技能訓練）様のセッションがある．認知矯正療法の手法の中には，これらを含んで1つの手法として成立しているものもある．言語セッションなどでは認知機能の，いわば応用が求められるため，原則として，注意，集中などの基本的な認知機能訓練が終了しているか，少なくとも並行して行われていることが望ましい．必要となる認知機能の種類や改善度は，SST 様のセッションや就労訓練では言語セッションより難易度が高くなると考えられる．

表　Chacracteristics of various cognitive remediation

標的領域の違い	特定神経認知，神経認知全般
理論的立場の違い	補償的観点，回復的観点
使用媒体	コンピューター，紙と鉛筆
般化のための手法	言語セッション，就労訓練，SST

認知矯正療法は認知機能障害の治療法であるが，精神疾患のリハビリテーション法でもあるため，患者の動機付けが重要視される．患者の動機付けを顕在化させ，認知矯正療法での課題の取り組みをより熱心にさせたり，精神疾患からのリハビリテーションや，治療全体に対してより主体的になることを狙いとしている．このような動機付けはコンピューター課題によるフィードバックでもなされるが，認知矯正療法セラピストによる言語的な介入や励ましがより効果的と考えられる．謝金を与え，動機付けをしている場合も，研究報告によってはある（Bell et al, 2001）が，これは現実の臨床場面での運営には困難をきたすことが予想され，実践されることは多くないと考えられる．

IV. 認知矯正療法の効果について

1. メタ分析

1）効果を報告している治療法

数ある認知矯正療法のうち，RCT 研究で治療効果が示されている主な手法と効果を以下に示す．Integrated Psychological Treatment（IPT）（Roder et al, 2006）は5段階で構成され，小集団形式で週1～3回施行する．認知機能（d=.48）と社会機能（d=.34）の改善が報告されており，治療終了8カ月後の効果持続が確認されている．国際的に様々な国で実施されているところが特徴である．

Neurocognitive and Educational Approach to Remediation（NEAR）（Medalia and Choi, 2009）はコンピューターセッションと言語セッションを用いて小集団形式で週2回施行する．教育原理を応用し内発的動機付けの促進を行う．認知機能（d=.34）と社会・就労機能（d=.14）改善効果は治療終了4カ月後の持続が確認されている（Hodge et al, 2010）．

Cognitive Enhancement Therapy（CET）（Hogarty et al, 1999）はコンピューターセッションと SST を組み合わせて小集団形式で行う．認知機能（d=.60）と社会機能改善（d=.37）が認められ，効果は治療終了1年後まで持続したことが報告されているが，訓練内容と評価検査の類似性などが限界点である．他の認知矯正療法では，SST など他のリハビリテーション手法が別に取り入れられているのに対して，認知矯正療法の一部としているところが特徴である．

Neurocognitive Enhancement Therapy（NET）（Bell et al, 2001）はコンピューターを用いた認知矯正と就労リハビリテーションを組み合わせて行う．認知機能（d=0.40）と