FUNCTIONAL CORTICAL AND COGNITIVE ABNORMALITIES IN FIRST-EPISTODE SCHIZOPHRENIA PATIENTS — IMPACT OF TRAINING

Dissertation zur Erlangung des akademischen Grades eines Doktors (Dr. rer. nat.)

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2. Referent: Prof. Dr. Thomas Elbert
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I. Abstract

Cognitive impairment is widely seen as a core symptom in schizophrenia patients. Emerging evidence shows that cognitive abnormalities arise in the early phases of the illness, which challenges the traditional view of cognitive decline or decay as a part of illness progression. This underlines the notion of cognitive impairment in schizophrenia as a manifestation of fundamental neurodevelopmental deficits. Evoked and induced event-related neural oscillations have recently been proposed as key mechanisms supporting higher-order cognition. It is not yet known whether altered event-related modulation of oscillatory activity is present at early stages of schizophrenia. Alterations in activity could reflect the early development of psychopathology. The objective of the present thesis was to explore the cognitive profiles and oscillatory dynamics associated with the double-click design in a sample of first-episode (FE) schizophrenia patients. As an indicator of disturbed neuronal signal resolution in the auditory system, M50 sensory gating was assessed. Sensory gating describes a neurological process of filtering out redundant information, for example the second of two identical stimuli in the double-click paradigm. This mechanism is proposed to contribute to cognitive functioning. In a second step of this thesis, an auditory computer-based cognitive training was applied and its influence on cognitive outcomes and oscillatory dynamics during the double-click paradigm was evaluated. Additionally, the training was compared to a different, but comparable facial affect recognition training in chronic patients to evaluated its specificity.

Study 1:

Cognitive deficits and abnormal electromagnetic sensory gating reliably distinguish schizophrenia patients from healthy controls. Study one investigated the extent to which abnormally high gating ratios, event-related modulation of oscillatory activity and cognitive deficits manifest at early stages of schizophrenia. Cognitive test performance (MATRICS Consortium Cognitive Battery, MCCB), neuromagnetic event-related fields (M50 gating ratio), and oscillatory dynamics (evoked and induced modulation of 8–12 Hz alpha) during a paired-click task were assessed in chronic and FE patients. Both patient groups displayed cognitive deficits, poorer sensory gating, and less induced modulation of alpha power, than healthy controls. Induced alpha power decrease in bilateral posterior regions varied with the M50 ratio in healthy controls but not in schizophrenia patients, whereas an orbitofrontal alpha power
decrease was related to the M50 ratio only in schizophrenia patients. Results suggest disruption of oscillatory dynamics at early stages of illness, which may contribute to deficient information sampling, memory updating, and higher cognitive functioning.

**Study 2:**
As cognitive deficits are seen as a core feature of schizophrenia, they form a major target of remediation strategies. Whilst patients respond moderately well to cognitive remediation, research is currently exploring variants in training, to further amplify these beneficial effects. The question was if targeted neuroplasticity-based training improves cognitive deficits more than nonspecific remediation, and whether there are differential effects on patients at different stages of the illness (FE and chronic patients). Participants received either four weeks of two targeted neuroplasticity-based training protocols or treatment-as-usual (TAU). Performance in the cognitive test battery was assessed before and after training, and again at 3-months follow-up. Performance improved across assessments independently of intervention type, phase of illness, or symptom remission, though did not reach normal levels. Factors augmenting remediation effects beyond targeting function and neuroplasticity-based learning remain to be scrutinized.

**Study 3:**
The similarity of cognitive deficits and dysfunctional brain activity between FE and chronic schizophrenia patients as demonstrated in the first study, suggests that early intervention is necessary to target these impairments. Cognitive training impacts cognitive function and functional decline, while the effects on their neuronal underpinnings remain to be substantiated. The third study evaluated effects of a neuroplasticity-based training targeting auditory-verbal discrimination and memory in FE patients. Effects on alpha activity as a measure of facilitated neuronal input processing were investigated. Patients’ alpha power decrease was significantly augmented, both immediately after and a further three months after targeted training, but not after TAU. The impact of targeted training demonstrated potential for cortical reorganization in FE, therefore demanding early, intense and targeted intervention.

**Study 4:**
Study four addressed neuronal signal resolution in the auditory system as a mechanism contributing to cognitive function and dysfunction in schizophrenia. Effects of two neuroplasticity-based training protocols targeting auditory–verbal or facial affect discrimination accuracy and a standard rehabilitation protocol on magnetoencephalographic (MEG) oscillatory brain
activity in an auditory paired-click task were compared. Patients initially showed abnormally small alpha decrease around the second stimulus (S2). This improved specifically after targeted auditory–verbal training, and not after either facial affect training or TAU. Results replicate previous findings and indicate specificity of cortical training effects.
II. Zusammenfassung


Evozierte und induzierte neuronale Oszillationen werden als ein Mechanismus angenommen, der kognitive Prozesse unterstützt oder ermöglicht. Zum jetzigen Zeitpunkt ist unklar, ob sich eine veränderte Modulation von Oszillationen bereits im frühen Krankheitsstadium manifestiert und somit die Entwicklung der Psychopathologie widerspiegelt.


Studie 1:

Patientengruppen zeigten kognitive Defizite, ein auffälliges gating-ratio und eine herabgesetzte Modulation der induzierten Alpha-Aktivität (8-12 Hz).


**Studie 2:**
Kognitive Funktionseinschränkungen werden als zentrales Merkmal schizophrener Erkrankungen gesehen und entsprechend in Behandlungskonzepten berücksichtigt. Kognitive Remediationsprogramme gelten als wirksam, Effektstärken aber als moderat.

In der zweiten Studie wurde untersucht, ob gezieltes Funktionstraining in einem Neuroplastizitäts-orientierten Lernkontext effektiver ist als ein breitgefächertes Behandlungsprogramm und ob die Effekte durch das Erkrankungsstadium (chronisch vs. ersterkrankt) moduliert werden.

Die kognitive Testleistung wurde vor und nach einer 4-wöchigen Interventionsphase mit zwei spezifischen Trainings (Experimentalgruppe) oder einer Standardbehandlung (Kontrollgruppe) sowie zur 3-monatigen Katamnese erfasst.

Sowohl chronische als auch erstmalig behandelte Schizophrenie-Patienten verbesserten ihre kognitiven Funktionen signifikant über die Messzeitpunkte, obwohl Defizite relativ zu den Kontrollprobanden fortbestanden. Die Verbesserungen waren unabhängig von Trainingsvariante und Krankheitsstadium.

**Studie 3:**
wurde die Desynchronisation im Alpha-Frequenzbereich im Doppel-Klick Design hinzugezogen. Die Alpha-Power-Reduktion um den zweiten Stimulus (S2) verbesserte sich direkt und drei Monate nach dem Training, nicht jedoch nach treatment-as-usual (TAU). Die Ergebnisse sprechen für das Vorhandensein eines Reorganisationspotentials bei ersterkrankten Patienten, was wiederum die Wichtigkeit früher und gezielter Interventionen unterstreicht.

**Studie 4:**
In der vierten Studie wurden zwei vom Aufbau her vergleichbare, Computer-basierte und Neuroplastizitäts-fördernde Trainings und TAU hinsichtlich ihrer Effekte auf die oszillatorische Gehirnaktivität im Doppel-Klick Design bei chronischen Patienten verglichen. Während im ersten Training die auditorisch-verbale Diskrimination im Vordergrund stand, basierte das zweite Training auf Affektdiskrimination. Die im Vergleich zu Gesunden auffällig schwächere Alpha-Power-Reduktion um den zweiten Stimulus (S2) verbesserte sich bei den Probanden deutlicher nach dem auditorisch-verbalen Training als nach Affektdiskriminations-Training oder TAU. Die Resultate replizieren die Ergebnisse vorangegangener Studien und deuten auf die Spezifität von kortikalen Trainingseffekten hin.
III. Conducted studies and own research contributions

The studies in the present thesis were co-authored and supported by a number of colleagues. They are listed below, together with my own contributions.

Study 1:
Functional cognitive and cortical abnormalities in chronic and first-admission schizophrenia


My contributions:
I collected the cognitive test data and electromagnetic data from chronic and FE patients, I had the major responsibility for analyses of oscillatory activity and MCCB analyses and prepared the manuscript and the figures.

Study 2:
Kognitive Defizite bei schizophren Erkrankten – Einfluss von Training


My contributions:
I collected the cognitive test data, trained the chronic and FE patients, conducted the analyses of the MCCB data and prepared the manuscript and the figures.

Study 3:
Neuroplasticity-based training modifies oscillatory activity in first-episode schizophrenia patients

In revision for Schizophrenia Research: Carolus, A. M., Schubring, D., Popov, T. G., Nischk, D.& Rockstroh, B. S. Neuroplasticity-based training modifies oscillatory activity in first-episode schizophrenia patients.

My contributions:
I conducted the patient trainings and the data collection (MCCB, MEG), contributed to data analysis and preparation of the manuscript

**Study 4:**

**Neuroplasticity-based training modifies oscillatory activity in first-episode schizophrenia patients**


**My contributions:**
I collected the cognitive test data and electromagnetic data from chronic patients, supervised the patient trainings and contributed to the analyses of oscillatory activity and MCCB data.
IV. Abbreviations

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<thead>
<tr>
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<tbody>
<tr>
<td>Att</td>
<td>Attention</td>
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<tr>
<td>BLIPS</td>
<td>Brief Limited Intermittent Psychotic Symptoms</td>
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<td>BDNF</td>
<td>Brain-Derived Neurotrophic Factor (BDNF)</td>
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<td>BFP</td>
<td>Brain Fitness Program</td>
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<td>CE</td>
<td>Cognitive Exercise</td>
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<td>CHR</td>
<td>Chronic</td>
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<td>CPZ</td>
<td>Chlorpromazine</td>
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<td>CRT</td>
<td>Cognitive Remediation Trainings</td>
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<td>DICS</td>
<td>Dynamic Imaging of Coherent Sources</td>
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<tr>
<td>DSM</td>
<td>Diagnostic and Statistical Manual</td>
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<td>EEG</td>
<td>Electroencephalography</td>
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<td>FA</td>
<td>First-Admission</td>
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<td>FAT</td>
<td>Facial Affect Training</td>
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<td>GAF</td>
<td>Global Assessment of Functioning</td>
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<td>HC</td>
<td>Healthy Control</td>
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<td>ICD</td>
<td>International Classification of Diseases</td>
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<td>IPT</td>
<td>Integrated Psychological Therapy</td>
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<td>IQ</td>
<td>Intelligence Quotient</td>
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<tr>
<td>M.I.N.I</td>
<td>Mini International Neuropsychiatric Interview</td>
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<tr>
<td>M100</td>
<td>Evoked magnetic field ~ 50 ms post stimulus</td>
</tr>
<tr>
<td>M50</td>
<td>Evoked magnetic field ~ 100 ms post stimulus</td>
</tr>
<tr>
<td>MATRICS</td>
<td>Measurement and Treatment Research to Improve Cognition in Schizophrenia</td>
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<td>MCCB</td>
<td>MATRICS Consortium Cognitive Battery</td>
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<td>MEG</td>
<td>Magnetoencephalography</td>
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<td>MNI</td>
<td>Montreal Neurological Institute</td>
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<tr>
<td>NMDA</td>
<td>N-Methyl-D-Aspartate</td>
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<tr>
<td>P300</td>
<td>Evoked positive potential ~300 ms post stimulus</td>
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<td>P50</td>
<td>Evoked positive potential ~50 ms post stimulus</td>
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<tr>
<td>PANSS</td>
<td>Positive and Negative Syndrome Scale.</td>
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<td>PFC</td>
<td>Prefrontal Cortex</td>
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<td>PS</td>
<td>Processing Speed</td>
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<td>Reas</td>
<td>Reasoning</td>
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<tr>
<td>S1</td>
<td>First Stimulus in the Double-Click Design</td>
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<td>S2</td>
<td>Second Stimulus in the Double-Click Design</td>
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<td>SAA</td>
<td>Serum Anticholinergic Activity (SAA),</td>
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<td>SC</td>
<td>Social Cognition</td>
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<td>STG</td>
<td>Superior Temporal Gyrus</td>
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<td>TAU</td>
<td>Treatment-As-Usual</td>
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<td>TT</td>
<td>Targeted Training</td>
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<td>VerL</td>
<td>Verbal Learning</td>
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<td>VisL</td>
<td>Visual Learning</td>
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<td>WM</td>
<td>Working Memory</td>
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**German Abbreviations**

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<tbody>
<tr>
<td>AG</td>
<td>Arbeitsgedächtnis</td>
</tr>
<tr>
<td>AM</td>
<td>Aufmerksamkeit</td>
</tr>
<tr>
<td>KG</td>
<td>(gesunde) Kontrollgruppe</td>
</tr>
<tr>
<td>SD</td>
<td>Schlussfolgerndes Denken und Problemlösen</td>
</tr>
<tr>
<td>SI</td>
<td>Soziale Intelligenz</td>
</tr>
<tr>
<td>VerbL</td>
<td>Verbales Lernen</td>
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<tr>
<td>VGS</td>
<td>Verarbeitungsgeschwindigkeit</td>
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<tr>
<td>VisL</td>
<td>Visuelles Lernen</td>
</tr>
</tbody>
</table>

xix
1. General Introduction

1.1. Schizophrenia: What affects onset and course?

Schizophrenia is a severe mental illness affecting about 1% of the population and associated with major social disability and far above-average treatment expenses (Clade, 2003; Frangou & Byrne, 2000). Still considered an enigma despite a century of research (Häfner, 2000) closer inspections on begin and course of symptoms is expected to improve understanding the origins and characteristics of this remarkably complex disorder. A growing body of evidence suggests that the early stages of schizophrenia are critical in determining the course and predicting the outcome of the disorder.

The longitudinal study (Mannheim ABC-Study, Age, Beginning and Course) launched by Häfner and colleagues in the eighties, (Häfner et al., 1998; Häfner et al., 2013) set off a great number of research projects on the prodromal state and the onset of psychosis. The population-based retrospective Mannheim ABC-study evaluated and observed FE patients retrospectively as well as prospectively. Unspecific symptoms were found in about 73% of the patients on average five years before the onset of the first psychotic episode. This phase was defined as the first stage, followed by the second stage, which starts with psychotic symptom development and lasts until the first hospitalization, on average 1.3 years later (Häfner & Maurer, 2006). Among the most frequent initial signs in the early stage of schizophrenia, Häfner and Maurer (2006) described restlessness, depression, trouble with thinking and concentration as well as social withdrawal, distrust and problems in communication, altogether symptoms that initiate the early process of functional and social decline. Based on the results of a retrospective survey in 128 first-episode (FE) patients Schultze-Lutter and colleagues (2010) proposed a model of symptom development, in which the prodrome typically starts off with unspecific mental problems (UN) combined with other risk factors (such as for example a family history with schizophrenia, substance abuse etc.) and functional decline, followed by basic symptoms (BS; subtle, subclinical self-experienced disturbances in thought, speech, and perception processes that are rarely perceivable from the outside). Subsequently, attenuated psychotic symptoms can occur (APS; ideas of reference, unusual perceptual experiences including body-related illusions, paranoid ideation/mistrust, magical thinking, and odd speech), which finally result in psychotic symptoms (PS). The chronological
sequence ‘UN-BS-APS-PS’ could be confirmed (Schultze-Lutter et al., 2010) and is depicted in figure 1.

In addition to understanding origins and development of the disorder, the devastating consequences on social and occupational outcome once the illness has started (Davidson et al., 1999; Häfner et al., 1999; Heinz Häfner & Maurer, 2006; Johnstone et al., 1990; Tsang et al., 2000) encouraged efforts to identify individuals with a high risk or an ultra-high risk of developing schizophrenia with the aim to prevent, ameliorate or delay the development of psychosis.

![Figure 1](image)

**Figure 1**
Course of subclinical psychosis until first psychotic episode (modified from Schulze-Lutter et al. 2010)

The first intervention studies aimed at preventing psychosis by means of cognitive behavioral therapy (CBT) started about 20 years ago. A reduction of prodromal symptoms as well as significantly fewer transitions to psychosis when compared to a control group could be demonstrated (Bechdolf et al., 2005; Lewis et al., 2002; McGorry et al., 2002). In his review, Singh (2010) emphasizes the need as well as the economic benefits of specialized early intervention programs: For example, the Danish OPUS trial, in which FE patients who participated in an intensive early intervention program were monitored over a period of five years,
spent less days in hospital than the patients that received standard treatment and a smaller percentage of them was living in supported housing (Bertelsen et al., 2008). These results are in line with the outcome of the ‘LEO’ intervention program in the UK (Craig et al., 2004). Still, there are controversies concerning the implementation of large-scale prevention programs with regard to costs as well as effectiveness. In the OPUS trial for example, most of the positive effects (reduction in positive and negative symptoms and global functioning, substance abuse) were not sustained after transference to standard treatment (Nordentoft et al., 2014). In order to tailor prevention, specific characteristics and determinants of onset and course should be clarified. As cognitive deficits and (related) brain parameters have been shown to be present already in early stages of the illness and therefore comprise a potential goal for treatment, they will be briefly discussed in the following sections.

1.2. Cognitive functioning in schizophrenia and the course over time

There is consensus that cognitive deficits are a core feature of schizophrenia (Elvevåg & Goldberg, 2000; Kahn & Keefe, 2013). Impaired cognitive functions have been associated with schizophrenia since Kraepelin coined the term ‘dementia praecox’ in 1919 (Berrios et al., 2003). ‘Dementia praecox’ or ‘premature dementia’ emphasized the rapid cognitive decline, disruption in memory, attention and cognitive functions.

Traditionally, cognitive impairments were thought to characterize chronic, elderly patients, and were assumed to progress with the illness. However, evidence accumulates that challenges this neurodegenerative view, as cognitive deficits manifest in any state of the illness and often even pre-date the onset of psychotic symptoms (O’Carroll, 2000). Some authors claim that not all patients show cognitive impairments (e.g., Palmer et al., 1997). However, defining cognitive impairment as a current level of functioning below the level expected for the age group and from premorbid estimates, more than 98% of patients fulfill this criterion (Keefe et al., 2005).

The terms ‘cognitive impairment’, ‘abnormal cognitive functioning’, ‘cognitive deficits’ or ‘abnormal executive functions’ are used interchangeably and do not specify the affected cognitive function. As it is still a topic of debate whether schizophrenia is characterized by a general deficit or a profile of specific dysfunctions instead, a simple listing of impaired functions is difficult (Gopal, 2005). A prominence of broad deficits in areas of memory, attention, and language have been confirmed by several meta-analyses (e.g. Fioravanti et al., 2012; Gopal, 2005, Heinrichs, 2004). Verbal memory is most consistently reported in early (FE pa-
tients) and late states (chronic patients; for review: Cirillo & Seidman, 2003; Heinrichs & Zakzanis, 1998). It has been associated with functional and occupational outcome and is therefore seen as a major target for treatment (Touloupiouand & Murray, 2004; Vinogradov et al., 2009).

Whereas it was traditionally thought that the patients’ cognition was subject to continuing decline with duration of illness, more recent longitudinal cohort studies show underperformance in many cognitive domains even in children who later developed schizophrenia (Reichenberg et al., 2010; van Oel et al., 2002). Also, cognitive deficits have been shown in individuals with an ultra-high risk in the same magnitude as in individuals with a familial risk to develop a psychosis (Üçok et al., 2013). This suggests that cognitive deficits are likely to be existent prior to the first episode of schizophrenia and that genetic contributions might play a role.

In order to clarify, whether cognitive deficits represent a core psychopathological marker or develop in the course of illness, longitudinal studies offer insight. These studies show that FE patients score 1-2 standard deviations below healthy comparison subjects. This difference remains stable over a period of up to 10 years, suggesting that neuropsychological impairment is already present at the onset of the illness and remains stable over time (Albus et al., 2006; Dickerson et al., 2014; Hill et al., 2004; Hoff et al., 1999, 2005; Kurtz, 2005; Rund, 1998). These findings are consistent with a neurodevelopmental rather than a neurodegenerative model of schizophrenia.

This accumulating evidence left its mark: it has been – and is still – discussed to include cognitive deficits into A criteria in DSM (Keefe, 2008; Tandon et al., 2013). But first of all, cognitive deficits should be increasingly considered as a primary target for treatment (Kahn & Keefe, 2013; Keefe & Fenton, 2007).

**1.3. Brain parameters prominent in the early course of illness**

In addition to and together with cognitive markers, structural and functional brain abnormalities lead the way to understanding the disorder. The traditional conceptualization of schizophrenia as ‘brain disorder’ (Griesinger, 1845) or ‘neurodevelopmental disorder’ (Weinberger, 1987) exemplifies the strong link between etiological and brain research. A comprehensive review of evidence regarding brain abnormalities in schizophrenia is beyond the scope of this thesis. Rather, the following paragraph briefly summarizes established
markers of early alterations that are discussed as fundamental pathophysiology or contributors to onset and course of symptomatology.

With regard to structural abnormalities, findings of progressive gray-matter loss, especially active in the early stages (Asami et al., 2012; Cannon et al., 2015; DeLisi, 2008; Salisbury et al., 2007; Sun et al., 2009; Vita et al., 2012) as well as disruption in white-matter structures (Cheung et al., 2011; Liu et al., 2013; Szaszko et al., 2005, 2010; Yao et al., 2013) starting early and progressing with the course of the illness, suggest early pathophysiology. Based on a recent meta-analysis, it seems evident that once psychosis is present in patients, many of the underlying biological processes (especially the decrease of white-matter volume) must have been ongoing for years, while there are other abnormalities that progress with duration of illness after onset (Haijma et al., 2013; Kahn & Sommer, 2015).

In the recent years the perception of the human brain as a highly active, self-organizing system with extreme complexity and mostly nonlinear dynamics has emerged. This notion has generated the idea of schizophrenia illness resulting from disturbed brain dynamics rather than from well-localized defects in specific brain areas (Uhlhaas & Singer, 2015). A great number of brain parameters have been examined in schizophrenia that supports this assumption. Former studies in our group focused on the M50 sensory gating (MEG analog of the EEG P50) as a fundamental indicator of disturbed auditory signal discrimination in schizophrenia (Popov et al., 2012, 2011 a, b). P50 sensory gating (footnote 1) was found to distinguish even better than cognitive performance between chronic patients and healthy controls with large effect sizes (Cromwell et al., 2008; Heinrichs, 2004).

Concerning the paired-click design, abnormalities in oscillatory activity had previously been reported for chronic patients. Popov and colleagues (2011 b) found a sequence of S1-evoked gamma power increase and induced alpha power decrease around S2, which was proposed to be a mechanism enabling efficient auditory gating. Smaller evoked and induced alpha power modulation in chronic and a relationship of abnormally high gating ratio with smaller alpha power modulation (see also Hall et al., 2011; Hamm et al., 2012) were interpreted as evidence for a less efficient involvement of the relevant neural networks supporting initial stimulus encoding, sustained attention, and comparison with stored memory. Except for Hall and colleagues (2011), who demonstrated a relation of reduced gamma activity after S1 and reduced beta activity after S2 with the age at illness onset, oscillatory characteristics of the P50 paradigm at different stages of illness (e.g. in FE schizophrenia patients) remain to be
specified. Findings of oscillatory and event-related abnormality already in early stages of illness should advance hypotheses on brain processes contributing to onset and course of psychopathology.

1.4. Amelioration of course and onset by intervention

In addition to pharmacological treatment – the effects of which are limited (Keefe et al. 2007, Woodward et al. 2005, Goldberg et al. 2007, Goff et al., 2011) – cognitive remediation programs have been developed and evaluated over the past 50 years for chronic (Grynszpan et al., 2011; Hodge et al., 2010; McGurk et al., 2007; Wykes et al., 2011) and FE patients (Barlati et al., 2012; Bechdolf et al., 2012). These programs comprise a variety of methods including drill and practice exercises, teaching and compensatory strategies and they consistently find positive but modest results (McGurk et al., 2007). The effects of remediation programs are sometimes assessed as a ‘quick fix’, thus lacking a demonstration of usefulness as long-term treatment (Pfammatter et al., 2006; Trapp et al., 2013), and effect sizes are considered low to medium (e.g. Keefe et al., 2012). Additionally, some authors claim that these programs do not have sufficient effects on the functional outcome, or that functional variables as an outcome measure have been neglected (McGurk et al., 2007; Wykes et al., 2011).

As duration of untreated psychosis (DUP) has been repeatedly shown to be related to longer time to remission, less remissions and more psychotic symptoms (de Haan et al., 2003), there is demand for a more specific trainings that concentrated on the impaired mechanisms and that are feasible for the patients as soon as possible after detection of the onset.

Two important paradigm shifts within the past years have influenced the development of a new rationale for training programs (that take into account neuro-scientific findings, i.e., target hypothesized basic pathophysiology or altered brain functions) that are relevant for FE patients, too: first, schizophrenia is mainly seen as a neurodevelopmental disorder, characterized by aberrant activation patterns and brain plasticity that are present before the onset of the illness. Second, abnormalities are not static but modifiable by interventions that target brain plasticity (Biagianti & Vinogradov, 2013). These paradigm shifts, combined with meta-analytic data about cognitive remediation and findings from basic and clinical neuroscience have resulted in a new understanding of the critical elements that should be incorporated when designing effective training programs to improve cognitive functioning in schizophrenia patients (for an overview see Merzenich et al., 2014).
Related to the development of trainings, a neuroscience-guided approach should consider implicit learning, repetitive practice, training of (basic) sensory processing to enhance responsiveness to cognitive training and to ensure that higher-order functions receive more reliable signals, a large number of trials that are individually adapted and a reward schedule to drive and enhance neuromodulatory responses (for an overview see Genevsky et al., 2010). An example of a training program following these recommendations is the ‘brain fitness program’ (BFP, Posit Science, SF, USA) which targets auditory processing (as verbal learning is one of the most impaired cognitive functions in schizophrenia; see chapter 1.2 in this thesis) and follows the principles of neuroplasticity massed practice, shaping, and motivating context (overview Elbert & Rockstroh, 2004). The computer-based training has been shown to improve verbal learning and memory measures (Fisher, 2009), with effects that lasted six months after intervention and with significant improvement of life quality (Fisher, 2010). First results also confirmed effectiveness in FE patients (Fisher et al., 2014). Importantly, training effects varied with changes in brain markers indicating an impact of psychological means on neurophysiological/electrocortical functions: Effects were reported on serum anticholinergic activity (SAA), reflecting medication induced anticholinergic burden, showed a significant negative correlation with cognitive improvement as well as an increase in serum brain-derived neurotrophic factor (BDNF) levels after training; both might reflect biomarkers for cognitive training (Vinogradov et al., 2009).

Effects of cognitive remediation trainings (CRT) on electrocortical measures have frequently been reported in chronic patients (for an overview see Thorsen et al., 2014). Specifically for BFP, Popov and colleagues (2012) found training-induced modification of oscillatory activity during the paired-click task.

The present thesis extended this database by evaluating training effects in FE patients: If cognitive deficits and altered brain function are evident in FE, this indicates pre-symptomatic psychopathology. The possibility to modify these altered brain functions by psychological intervention would advocate normalization of brain abnormalities as target of intervention.

1.5. The rationale of the present thesis

The main objective of the present thesis was to test the hypotheses that a) cognitive deficits and brain parameters that are related to basic perceptual processing are evident already early in the course of illness and therefore not the consequence of chronicity and long-term
(medication) treatment and b) that these cognitive deficits and altered brain parameters can be modified by a computer-based cognitive training.

The first hypothesis was tested by comparing a group of FE to a group of chronic schizophrenia patients in the above-named parameters. To test the second hypothesis, the cognitive functions and brain parameters of FE patients, who participated in the computer-based cognitive training, were compared to the parameters of FE patients, who received treatment-as-usual. Additionally, the specificity of the auditory training on cortical changes was evaluated.

The present thesis addresses these hypotheses in four different chapters:

1. **Functional cognitive and cortical abnormalities in chronic and first-admission schizophrenia:**
   Chapter two of this thesis discusses the cognitive profiles (as assessed with the MATRICS Consortium Cognitive Battery (MCCB)) and cortical abnormalities that are observable during the double-click-design in the MEG in FE schizophrenia patients and compares the results to the characteristics of a chronic sample. A precise characterization of the abnormalities in young FE patients allows gaining insight into the development of the illness and is of vital importance when it comes to parameters that should be targeted by trainings.

2. **Cognitive deficits in schizophrenia – impact of training** (article in German: Kognitive Defizite bei Schizophren Erkrankten – Einfluss von Training)
   Chapter three focusses on the cognitive domains in both groups, the chronic and FE patients, and includes the factor time (pre-, post- and follow-up assessment) and training (Brain Fitness Program vs. treatment-as-usual in FE patients, Brain Fitness Program vs. Affectdisrimination training vs. treatment-as-usual in chronic patients). It aims to answer two different questions. First: Are there specific training effects on any of the cognitive domains? Second: Are there any differences in the change over time if we include the status of the illness (chronic vs. FE) in the analysis?

4. **Neuroplasticity-based training modifies oscillatory activity in first-episode schizophrenia patients**
The fourth chapter of this thesis focuses on computer-based training in FE patients. It intends to answer the following questions: do FE patients who accomplish targeted computer-based training show larger changes in electromagnetic responses in the paired-stimulus design and cognitive test performance than FE patients undergoing treatment-as-usual? And if so, are these training-induced changes similar to those previously demonstrated in chronic schizophrenia patients?

3. Targeted training modifies oscillatory brain activity in schizophrenia patients

In chapter five of this thesis, the analysis that compares the effects on brain and cognitive measures of the two different trainings and TAU is presented. The aim was to replicate previous findings (Popov et al., 2012, 2011) and to underline the specificity of cortical training effects.
2. Functional Cognitive and Cortical Abnormalities in Chronic and First-Admission Schizophrenia

2.1. Abstract

Evoked and induced event-related neural oscillations have recently been proposed as a key mechanism supporting higher-order cognition. Cognitive decay and abnormal electromagnetic sensory gating reliably distinguish schizophrenia (SZ) patients and healthy individuals, demonstrated in chronic (CHR) and first-admission (FA) patients. Not yet determined is whether altered event-related modulation of oscillatory activity is manifested at early stages of SZ, thus reflects and perhaps embodies the development of psychopathology, and provides a mechanism for the gating deficit. The present study compared behavioral and functional brain measures in CHR and FA samples. Cognitive test performance (MATRICS Consortium Cognitive Battery, MCCB), neuromagnetic event-related fields (M50 gating ratio), and oscillatory dynamics (evoked and induced modulation of 8–12 Hz alpha) during a paired-click task were assessed in 35 CHR and 31 FA patients meeting the criteria for ICD-10 diagnoses of schizophrenia as well as 28 healthy comparison subjects (HC). Both patient groups displayed poorer cognitive performance, higher M50 ratio (poorer sensory gating), and less induced modulation of alpha activity than did HC. Induced alpha power decrease in bilateral posterior regions varied with M50 ratio in HC but not SZ, whereas orbitofrontal alpha power decrease was related to M50 ratio in SZ but not HC. Results suggest disruption of oscillatory dynamics at early stages of illness, which may contribute to deficient information sampling, memory updating, and higher cognitive functioning.
2.2. Introduction

Cognitive deficits have been reported in first-admission (footnote 2) patients with schizophrenia (e.g., Heinrichs, 2004, Mesholam-Gately et al., 2009, Wobrock et al., 2009, Bechard-Evans et al., 2010 and Fromman et al., 2011), with few specific functions distinguishing chronic (CHR) and first-admission (FA) samples (Hilti et al., 2010, Holmén et al., 2010 and Kelleher et al., 2013). Whereas cognitive performance measures have the virtue of likely being relatively close to the clinical symptoms that define schizophrenia, structural and functional brain measures are believed to be closer to the genetic contributors. Given that the causal story in schizophrenia is likely to be complex (Kessler, 2005 and Miller, 2010), interest is growing in psychological and biological endophenotypes, which are expected to reveal intermediate mechanisms in mental illness (Gottesman and Gould, 2003 and Miller and Rockstroh, 2013). Findings of gray-matter loss (Salisbury et al., 2007, DeLisi, 2008, Sun et al., 2009a, Sun et al., 2009b and Asami et al., 2012) as well as disrupted white-matter integrity (Liu et al., 2013) starting early and progressing with course of illness suggest early pathophysiology. Among the brain measures evaluated as most robustly distinguishing schizophrenic and healthy individuals, P50 sensory gating (footnote 3) has been found to produce even larger effect sizes than cognitive performance measures (Heinrichs, 2004). Abnormal sensory gating has been reported early in the development of schizophrenia (Brockhaus-Dumke et al., 2008, Keri et al., 2010 and Yee et al., 2010), though less consistently than cognitive deficits (e.g., deWilde et al., 2007 and Bachmann et al., 2010).

Electromagnetic oscillatory dynamics, proposed as indicating information flow within and across neural networks (e.g., Jensen and Mazaheri, 2010 and Buzsaki and Watson, 2012), may be promising endophenotypes for mental illness (e.g., Uhlhaas et al., 2008, Uhlhaas and Singer, 2010, Uhlhaas, 2011, Uhlhaas and Singer, 2012 and Buzsaki et al., 2013). Reduced evoked and induced activity in schizophrenia patients has been reported in higher (60–80 Hz, gamma) and lower (4–7 Hz, theta) frequency bands (Uhlhaas et al., 2008 and Woo et al., 2010). Evidence of oscillatory abnormalities in schizophrenia has been largely confined to CHR samples. The few studies involving FA patients indicate similar abnormalities in theta (e.g., Missonnier et al., 2012) and gamma activities (e.g., Symond et al., 2005, Haenschel et al., 2009 and Minzenberg et al., 2010). Analyzing event-related (M50 gating ratio) and oscillatory measures in the paired-click design, Popov et al. (2011) reported a sequence of S1-evoked gamma power increase and induced alpha power decrease around S2, which was
proposed as a mechanism enabling efficient auditory gating. Smaller evoked and induced alpha power modulation in CHR and a relationship of abnormally high gating ratio with smaller alpha power modulation (see also Hall et al., 2011 and Hamm et al., 2012) were interpreted as an evidence of less efficient engagement of relevant neural networks supporting initial stimulus encoding, sustained attention, and comparison with stored memory traces.

To evaluate the hypothesis that the abnormalities reported in Popov et al. (2011) in CHR manifested early in the illness, the present study compared cognitive test performance and neuromagnetic activity in CHR and FA samples. The first two specific predictions were framed to reject that hypothesis. (1) CHR will perform worse than FA on standard cognitive tests, perhaps reflecting chronicity and/or long-term neuroleptic treatment rather than abnormal processing fundamental to schizophrenic psychopathology. (2) CHR will show high M50 ratios (poor gating) and abnormal oscillatory dynamics, whereas FA will show M50 ratios and oscillatory dynamics similar to those of HC. (3) M50 ratios and oscillatory dynamics will correlate, providing evidence that oscillatory dynamics reflect fundamental aspects of neural information processing that contribute to cognition.

2.3. Methods and Material

Participants: Sixty-six inpatients were diagnosed by experienced senior psychiatrists or psychologists using ICD-10 criteria and recruited from the CHR and FA inpatient units of the regional Center for Psychiatry. Based on hospitalization records, 35 CHR had 3 to 20 inpatient admissions (footnote 4), and 31 FA were diagnosed and hospitalized for the first time. ICD 10 Diagnoses for CHR were *n* = 30 with paranoid-hallucinatory schizophrenia (F20.0); *n* = 4 with schizoaffective disorder (F25.1); *n* = 1 with psychotic episode (F23.2). The FA group consisted of *n* = 24 with F20.0, *n* = 3 with F25.1, *n* = 2 with F23.1, and *n* = 2 with F23.2. First experiences of positive symptoms in FA were reported to be on average of 8.7 weeks (range 1–52) before admission. The samples did not overlap with those of Popov et al. (2011 b).

Inclusion criteria for patients were normal intellectual function and no history of neurological condition or disorder, including epilepsy or head trauma with loss of consciousness. At the time of the laboratory assessment, clinical status was characterized by Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987) symptom score and Global Assessment of Functioning (GAF, DSM-IV Axis V). Patient groups (Table 1) did not differ in gender distribution, IQ (assessed by a standard German test for premorbid intelligence, MWT-B; Lehrl,
2005), years of education, or symptom scores. As expected, FA patients were younger than CHR patients. None of the FA patients had been treated with neuroleptics before admission, but all had started neuroleptic medication by the time of the assessment. CHR and FA patients did not differ in current chlorpromazine equivalent (CPZ).

**Table 1** Demographic and clinical sample characteristics.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>CHR (n= 35)</th>
<th>FA (n= 31)</th>
<th>CHR vs. FA</th>
<th>HC (n= 28)</th>
<th>SZ vs. HC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>33.5±7.3</td>
<td>21.6±3.</td>
<td>F&lt;1</td>
<td>29.3±9.5</td>
<td>n.s.</td>
</tr>
<tr>
<td>Gender (f/m)</td>
<td>25/10</td>
<td>21/10</td>
<td>Chi² &lt; 1 n.s.</td>
<td>14/14</td>
<td>Chi² = 2.4, p &gt;.1</td>
</tr>
<tr>
<td>IQ</td>
<td>11.1±1.8</td>
<td>10.7±1.7</td>
<td>F &lt; 1</td>
<td>12.5±1.0</td>
<td>F&lt;1.76 = 19.76**</td>
</tr>
<tr>
<td>GAF</td>
<td>102.8±15</td>
<td>102.7±13</td>
<td>F &lt; 1</td>
<td>102.7±13</td>
<td></td>
</tr>
<tr>
<td>PANSS P</td>
<td>45±14</td>
<td>52±14</td>
<td>F&lt;1</td>
<td>52±14</td>
<td>F&lt;1.63 = 5.12*</td>
</tr>
<tr>
<td>PANSS N</td>
<td>15.5±5.2</td>
<td>15.5±3.0</td>
<td>F &lt; 1</td>
<td>15.5±3.0</td>
<td>F&lt;1.63 = 1.70 n.s.</td>
</tr>
<tr>
<td>PANSS G</td>
<td>19.0±6.2</td>
<td>16.8±7.1</td>
<td>F&lt;1</td>
<td>16.8±7.1</td>
<td>F&lt;1.63 = 1.36 n.s.</td>
</tr>
<tr>
<td>CPZ</td>
<td>36.6±6.9</td>
<td>35.5±7.8</td>
<td>F&lt;1</td>
<td>35.5±7.8</td>
<td>F&lt;1.63 = 1.36 n.s.</td>
</tr>
</tbody>
</table>

*Note: Means ±SD. CHR, chronic schizophrenia sample. FA, first-admission schizophrenia sample. SZ, schizophrenia patient sample. HC, healthy comparison sample. GAF, Global Assessment of Functioning. PANSS, Positive and Negative Syndrome Scale. CPZ, Chlorpromazine equivalent. **: p< .01, *: p< .05, n.s.: p > .1

Twenty-eight healthy comparison subjects (HC) were recruited to be demographically comparable to the SZ sample. HC were screened with the Mini International Neuropsychiatric Interview (Ackenheil et al., 1999) to exclude psychiatric or neurological disorder. HC did not differ from SZ in gender distribution or age (Table 1). HC had 1.6 more years of education than SZ.

Participants provided written informed consent prior to the study, which comprised two sessions (cognitive testing and MEG paired-click task). They received 30 Euro upon completion. The study was approved by the ethics committee of the University of Konstanz.

**Cognitive Performance Assessment and Analysis:** The MATRICS Consortium Cognitive Battery (MCCB, Nuechterlein and Green, 2006) was used for the assessment of cognitive performance. The MCCB covers domains of cognitive functions that have been shown to be impaired in schizophrenia, including processing speed, attentional vigilance, working memory,
verbal learning, visual learning, reasoning, and social cognition. Raw scores were converted to T-scores based on a USA representative community sample of healthy subjects (Nuechterlein and Green, 2006; German norms have not been developed). Normal distribution was verified by the Kolmogorov–Smirnov test. Group differences in the mean T-scores for each domain and for an overall composite score were evaluated by ANOVAs using two a priori orthogonal between-subject contrasts: comparing SZ and HC (MCCB data available for 25 of the 28 HC) and comparing the two patient samples. These were used in a Group × Domain analysis, with the within-subject factor Domain comparing the seven cognitive domains using Huynh–Feldt epsilon correction. The comparison of SZ and HC served to replicate reported abnormalities in schizophrenia. The comparison of CHR and FA addressed the main hypothesis about abnormalities that manifest early in the course of disease. Significant main effects and interactions were followed up with appropriate comparisons.

**Neural Activity Assessment and Analysis**

**Paired-click design:** Prior to MEG measurement, individual hearing levels were determined for each ear separately via an adapted method of limits (Gescheide, 1997). The paired-click procedure comprised 100 pairs of 3 ms square-wave clicks (S1 and S2) presented with a 500 ms onset-to-onset interstimulus interval and a variable offset to onset interval of 7 to 9 s. Clicks were presented 60 dB above individual hearing level and delivered via 5 m non-ferromagnetic tubes. No performance task was involved, except that participants were asked to keep their eyes focused on a small fixation point throughout the procedure.

**Neuromagnetic data acquisition and analyses:** Details of MEG data collection and analysis were described in Popov et al. (2011) and in In the supplement: method details. For artifact-free trials (on average 95 trials/participant with no group differences: CHR 95.3 ± 5.5; FA 93.6 ± 9.8; HC 95.5 ± 5.3; F < 1), epochs of 1000 ms before and 2000 ms following the first click (S1) were extracted from continuous recordings. M50 was scored from epochs extending 100 ms before and 400 ms after each click (S1 and S2). Neural sources were estimated by fitting a pair of regional sources simultaneously in the left and right hemispheres for a 20 ms interval centered around the strongest peak prior to M100. Only solutions exceeding at least 75% goodness of fit (mean ± SD 92.7 ± 4.5%) for sources located in superior temporal gyrus were considered for analysis. As three CHR did not meet this criterion, results are reported
for 32 CHR, 31 FA, and 28 HC. Gating ratio was computed as the S2 M50 source strength divided by the S1 M50 source strength. Group differences in M50 gating ratio as well as in S1 and S2 were evaluated using orthogonal Group × Hemisphere ANOVAs (SZ vs. HC; CHR vs. FA) similar to those described above.

Time-frequency representations of power were scored from artifact-free epochs (CHR: 94.5 ± 4.2, FA: 95.9 ± 3.1, HC: 94.0 ± 3.0, F(2,91) = 2.33, p = .1) extending from 500 ms before to 1000 ms after S1. Based on spectral analysis computed for each trial, relevant time-frequency windows were determined by applying a cluster-based, one-tailed independent-sample t-test with Monte Carlo randomization (Maris and Oostenveld, 2007) to the sensor data. The same cluster-based independent-sample t-test statistics were used to look at potential group differences in power spectra in a 2-second pre-stimulus baseline. Source analyses were based on a frequency-domain adaptive spatial filtering algorithm enabling the dynamic imaging of coherent sources (DICS; Gross et al., 2001 and Popov et al., 2011). The time windows and frequency bands of interest used in the source-level analysis were based on results obtained from sensor-level analysis. Volume conduction modeling of the head was based on individual structural MRIs (available for 27 SZ and 21 HC) and on an affine transformation of an MNI-template brain (Montreal Neurological Institute, Montreal, Canada http://www.bic.mni.mcgill.ca/brainweb) to the subject's digitized individual head shape (Popov et al., 2011).

Relationships between change in alpha power from baseline per voxel and M50 gating ratio were probed with Pearson's correlations. For group comparisons of these relationships, the voxel with maximum correlation within significant clusters was identified as representing the cluster. The respective voxels were selected for each group, and the respective group-specific correlation coefficients were compared for SZ and HC and for CHR and FA using Fisher (1921) z transformations.

2.4. Results

**Cognitive performance:** As evident in Figure 2 and Table 2, MCCB performance was significantly poorer in SZ than in HC in all domains. FA performed better than CHR in social cognition, with poorer scores in all other domains, some significantly.
Figure 2
Box plots (including distribution of individual data points) of MCCB performance. T-scores for the domains processing speed (PS), attention (Att), working memory (WM), verbal learning (VerL), visual learning (VisL), reasoning (Reas), and social cognition (SC), plotted separately for chronic patients (CHR), first admission patients (FA), and healthy comparison subjects (HC). Asterisks indicate CHR≠FA at p <.05.

Table 2 Inferential statistics.

<table>
<thead>
<tr>
<th></th>
<th>SZ vs. HC</th>
<th>CHR vs. FA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MATRICS Omnibus Effects</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group</td>
<td>( F_{1,86} = 51.03^{**} )</td>
<td>( F_{1,64} = 2.56 ) p = .11</td>
</tr>
<tr>
<td>Domain</td>
<td>( F_{6,516} = 15.04^{**} ) e = .90</td>
<td>( F_{6,384} = 10.63^{**} ) e = .99</td>
</tr>
<tr>
<td>Group × Domain</td>
<td>( F_{6,516} = 3.70^{**} ), e = .93</td>
<td>( F_{6,384} = 4.02^{**} ), e = .99</td>
</tr>
</tbody>
</table>

**Group Simple Effects by MATRICS Domain**

|                         |            |            |
| Processing Speed        | \( F_{1,89} = 46.97^{**} \) | \( F_{1,64} = 5.36^{*} \) |
| Attention               | \( F_{1,89} = 10.83^{**} \) | \( F_{1,64} = 1.58 \) n.s. |
| Working memory          | \( F_{1,89} = 25.28^{**} \) | \(< 1 \) n.s. |
| Verbal learning         | \( F_{1,89} = 32.65^{**} \) | \(< 1 \), n.s. |
| Visual learning         | \( F_{1,89} = 19.80^{**} \) | \( F_{1,64} = 2.86^{+} \) |
| Reasoning               | \( F_{1,89} = 8.33^{**} \) | \( F_{1,64} = 9.80^{**} \) |
| Social cognition        | \( F_{1,89} = 18.22^{**} \) | \( F_{1,64} = 4.37^{*} \) |

**Gating Ratio**

|                         |            |            |
|                         | \( F_{1,89} = 11.85^{**} \) | \( F_{1,64} < 1 \) n.s. |

*Note*: **: p< .01, *: p< .05, +: p< .1, n.s.: p> .1
**M50 sensory gating ratio:** In the absence of Hemisphere and Group × Hemisphere effects, group comparisons were based on the cross-hemisphere mean M50 ratio. (Analyses were also done for each hemisphere separately, with similar results.) SZ exhibited higher M50 ratios than did HC (Fig. 3 and Table 2). The two patient samples did not differ. M50 ratio effect sizes in CHR (d = .79) and FA (d = .87) relative to HC were similarly high. Separate evaluation of S1- and S2-evoked M50 amplitude found no differences between SZ and HC (Group, Group × Hemisphere). FA exhibited smaller S1-evoked and marginally smaller S2-evoked M50 than CHR (F(1,61) = 5.38, p < .03; F(1,61) = 3.81, p < 0.1). For the entire sample, cross-hemisphere correlations for S1 M50, S2 M50, and M50 ratio were r = .23, .32, and .21, all at least p < .05. M50 ratio varied with processing speed (−.38), working memory (−.21), and verbal learning (−.29), all at least p < .05. These test measures did not vary with S1- or S2-evoked M50 amplitude, that is, with processes specifically related to stimulus encoding or memory-trace retrieval.

![Figure 3](image)

**Figure 3**
Box plot (including distribution of individual data points) of M50 ratio averaged across hemispheres separately for chronic (CHR) patients, first-admission patients (FA), and healthy comparison subjects (HC).
Oscillatory dynamics: Time-frequency representation of power changes (Fig. 4A) indicates evoked 5–8 Hz and 12–15 Hz power increases immediately following S1 and induced 8–12 Hz power decrease around S2 (400–800 ms after S1 onset). Groups did not differ in S1-evoked alpha power increase. HC had a larger increase in the 3–8 Hz range in a fronto-central sensor cluster (p < .001) 0–300 ms after S1 onset than did SZ.

Figure 4
(A) Time-frequency representations of 5–20 Hz power changes (% change from baseline) from 200 ms pre-S1 to 1000 ms post-S1 averaged across sensors for healthy comparison subjects (HC) and schizophrenia patients (SZ). S1 and S2 onsets were at 0 and 500 ms.
(B) Source reconstruction of 8–12 Hz power decrease averaged across 400–800 ms, thus around S2 (blue-shaded area in A). To highlight the sources of alpha ERD, only negative values are plotted, the opacity ranging from zero (transparent) to the most negative value observed (opaque). Color bar for A and B indicates changes in source power relative to baseline.
(C) Statistically significant HC vs. SZ group differences in sensor space (left panel) and source space (right panels) averaged across 400–800 ms. Planes in B and A are plotted at MNI coordinates for the activity minimum: x 45, y −25, and z 5, corresponding to BA 41 and 42.
Around S2, SZ showed much less induced 8–12 Hz decrease than did HC (p < .001). Source reconstruction (4B) confirmed that induced alpha power decrease was localized primarily to right-hemisphere temporo-parietal regions. Statistical differences at the sensor level (4C left panel) and in source reconstruction (Fig. 4C right panel) confirmed more alpha power decrease in HC than in SZ in bilateral temporo-posterior and occipital regions. CHR and FA did not differ in 8–12 Hz modulation (Fig. 5). S1-evoked 3–8-Hz power increase and induced alpha power decrease around S2 were independent. There was no significant difference between HC vs. SZ and CHR vs. FA during the 2-second pre-stimulus baseline in any frequency band.

![Figure 5](A) and (B) as in Fig. 4 but for chronic (CHR) and first-admission (FA) patients. No statistical group differences are displayed (which would parallel to Fig. 4 C), as no regions of significant differences between CHR and FA were found.

**Correlations with oscillatory dynamics:** In HC, larger induced alpha power decrease varied with smaller (more normal) M50 ratio (r = .62, p < .01) in bilateral posterior and temporo-parietal regions (Fig. 6A). In SZ, there was no relationship (r = −0.05, n.s.; SZ vs. HC z = 2.84, p < 0.01). CHR and FA correlations did not differ (z = 0.36, n.s.).

In contrast to these posterior regions, SZ exhibited a correlation between alpha power and M50 ratio in a bilateral orbitofrontal cluster (Fig. 6B; r = .30, p = 0.02), which was not evident in HC (r = .02, n.s.). CHR (r = .40, p = 0.02) and FA (r = .20, n.s.) did not differ significantly.
Figure 6

(A) Top: Correlations between M50 ratio and induced alpha power 400–800 ms after S1-onset in individual voxels within significant (corrected p < .05) voxel cluster for healthy comparison subjects (HC) and schizophrenia patients (SZ). Bottom: Scatterplot relating induced alpha power change from baseline 400–800 ms after S1 onset to M50 gating ratio in the temporo-occipital voxel cluster (red oval in A). MNI coordinates for the maximum voxel within the clusters x = 60, y = 70, and z = 5, corresponding to BA 19 and 37. Each square represents one subject. Blue: CHR, chronic patients; red: FA, first-admission patients; green: HC, healthy comparison subjects.

(B) Same as panel A but for orbitofrontal voxel cluster. MNI coordinates for the maximum voxel within the clusters (red oval): x = 5, y 34, and z = 27, corresponding to BA 11.

2.5. Discussion

The present results provide evidence of cognitive deterioration, reduced sensory gating, and disruption of related oscillatory dynamics in FA similar to those in CHR. Popov et al. (2011) proposed that evoked and induced oscillatory activity, particularly in the alpha frequency range, contributes to altered sensory gating in CHR. The present results support this proposal and show that these alterations are present already in FA patients.

The results demonstrate striking similarities in behavioral and neuromagnetic abnormalities in CHR and FA. The patient groups differed little in cognitive test performance, and both showed abnormally high M50 gating ratio and smaller induced alpha power decreases. The present CHR/FA comparison replicates in a single study the cognitive performance deficits separately reported in CHR (e.g., Heinrichs, 2004) and FA (e.g., Mesholam-Gately et al., 2009) as well as abnormal sensory gating in CHR (e.g. Patterson et al., 2008) and FA (e.g.,
Yee et al., 2010). Thus, both types of abnormality arise early in the disorder rather than being a product of chronicity. The present study adds evidence of abnormal modulation of alpha oscillations and suggests that this proposed mechanism of information sampling and memory-trace updating is dysfunctional early in the course of illness and underlie the gating deficit.

**Cognitive test performance:** Studies have reported relationships between P50/M50 and cognitive measures, in particular working memory and attention (e.g., Thoma et al., 2003 and Smith et al., 2010). The present results for the entire SZ sample are in line with the reported results. Better performance might have been expected from FA than CHR patients, but their younger age and more extensive education did not compensate for impaired cognitive function. Slower processing speed in FA might be attributed to the dampening effects of newly commenced neuroleptic treatment, although such slowing has also been reported for untreated adolescents who reported psychotic symptoms (Kelleher et al., 2013). Evidence of pharmacological treatment improving cognitive deficits is mixed (Goff et al., 2011), and cognitive improvement with neuroleptic treatment could be mediated by symptom improvement. The present patient samples differed in duration of neuroleptic treatment, though not in current medication (CPZ) nor symptom scores. Larger samples may be needed to identify a contribution of factors like symptom severity or medication to cognitive performance.

**Functional brain measures:** Replicating previous findings, the M50 ratio index sensory gating was abnormally high in SZ. In line with Yee et al. (2010), CHR and FA did not differ in gating. Several studies have related the larger P50/M50 gating ratio in SZ to inadequate S1 encoding, reflected in smaller S1-evoked P50/M50 or N100/M100 amplitude (e.g., Clementz and Blumenfeld, 2001, Smith et al., 2010, Chen et al., 2013 and Hamm et al., 2014). The present study confirmed this only for FA patients. If reliable, this developmental specificity would indicate an encoding deficit early in the course of the disorder, which might influence S2 processing or gating later in the disorder. However, the present lack of parallel (smaller) S1-evoked alpha power modulation does not support the hypothesis of an encoding deficit. Establishing that the present samples showed the typical gating abnormality sets the stage for exploring oscillatory phenomena as a possible mechanism for the gating deficit. Oscillatory dynamics proved to be abnormal in the SZ sample. Event-related modulation of oscillatory activity, in particular near the alpha range, has been associated with information processing and communication between neuronal networks (e.g., Jensen and Mazaheri, 2010,
Buzsaki and Watson, 2012 and Hanslmayr et al., 2012). Buzsaki and Watson (2012) proposed that induced alpha power decrease reflects facilitated information sampling (thereby creating a preparatory state for processes like stimulus encoding and memory-trace updating). The present comparison confirmed dysfunctional alpha power decrease in FA and in CHR.

The interpretation of alpha power advocated by Popov et al. (2011) suggests the relationships that manifest in correlations with M50 ratio. In the present study these relationships were region- and group-specific: a significant relationship between right temporo-parietal alpha power decrease and M50 ratio was found in HC, not SZ, and a significant relationship between inferior frontal alpha power modulation and M50 ratio was found in SZ, not HC. These distinct modulations in temporo-parietal and frontal regions are consistent with MEG results by Chen et al. (2013) using a similar standard paired-click design. They found inferior frontal gyrus activity in addition to the typical M50 dominance in bilateral temporal regions (STG). Chen et al. (2013) described a frontal articulatory system that activates a network spanning STG and PFC. Insufficient preparatory modulation by this system of secondary auditory regions (manifested in temporo-parietal alpha power modulation) seen in present SZ may undermine the functional relationship with the event-related M50 ratio. In addition, the relationship between frontal alpha power decrease and M50 ratio in SZ suggests a compensatory role for frontal processing. Perhaps this relationship was not seen in HC because of low M50 ratio variability.

P50 gating has been discussed as an endophenotype of SZ (summary Miller and Rockstroh, 2013), and the present findings that FA resemble CHR are consistent with this. However, the present study did not consider all criteria necessary to evaluate endophenotype status. Moreover, recent GWAS with large samples are not consistent in confirming genetic relationships with P50 gating (e.g., Greenwood et al., 2013 and Hall et al., 2014).

Medication effects are almost always a challenge in research on schizophrenia. The present similar abnormalities in CHR and FA argue against the present findings being secondary to long-term medication use. Although groups differed in the length of neuroleptic treatment (days versus years), pharmacodynamic activity at synaptic and neurotransmitter levels is expected, as changes indicated by blood serum levels are established within days. Normalization of sensory gating by neuroleptics has been found (Yee et al., 1998, Devrim-Ucok et al., 2008 and Oranje et al., 2013) or not (Hong et al., 2009) as in the present study. An impact of
medication on the present results cannot be ruled out but appears to be secondary to the impact of abnormal neuronal processes supporting information processing.

The fronto-central S1-evoked gamma and alpha power increase in fronto-central regions in SZ was smaller (in fact non-significant) than those reported in Popov et al. (2011). Processes associated with evoked activity such as top-down modulation of initial auditory information processing and S1 encoding may be less affected by the developing pathology than the attention-engagement and information-sampling processes related to induced alpha modulation. The finding of reduced S1-evoked theta activity in patients, similar to the results of Hamm et al. (2014), suggests deficits in attention-orienting responses or long-range connectivity that might be crucial for ‘gating in’ of S1 (Moran et al., 2012). As an alternative, such attentional processes and memory-trace updating may be more important for efficient stimulus discrimination, hence sensory gating, than S1-evoked processes.

2.6. Conclusion

Popov et al. (2011) proposed evoked and induced oscillatory activity, particularly in the alpha frequency range, as a mechanism contributing to the M50 gating ratio. The present results support this proposal and suggest that this mechanism is already disrupted in schizophrenia early in the course of disorder. Replicating the 2011 study in the present new sample, correlations between orbito- and mid-frontal alpha power and M50 ratio were found in SZ but not in HC. Yet to be determined is whether these group- and region-specific associations indicate that recruitment of neuronal networks is simply weakened in patients or instead inefficiently regulated. That is, fronto-central networks may be recruited in preparation for information sampling and attention deployment, which is inefficient for preparation of networks relevant for auditory stimulus processing in the paired-stimulus design and insufficient to compensate for dysfunction in such networks (e.g., Edgar et al., 2008).

3.1. Zusammenfassung


Fragestellung: Ist gezieltes Funktionstraining in neuroplastizitäts-orientiertem Lernkontext effektiver als breitgefächertes Behandlungsprogramm und werden Effekte durch das Erkrankungsstadium moduliert?

Methode: Bei 59 chronisch und 31 ersthospitalisierten schizophren Erkrankten wurden kognitive Defizite über Testleistungen der MATRICS Consensus Cognitive Test Battery gegenüber 25 gesunden Kontrollpersonen erfasst. Testleistungen vor, nach 4-wöchiger Interventionsphase mit zwei spezifischen Trainings oder Standardbehandlung und 3-monatiger Katamnese prüften den Einfluss von Interventionstypus und Erkrankungsstadium auf Leistungsverbesserung.

Ergebnisse: Sowohl chronische wie erstmals behandelte Patienten aller Behandlungsgruppen verbesserten sich signifikant über die Messzeitpunkte, obwohl Defizite relativ zu Kontrollen fortbestanden.

Schlussfolgerungen: Spezifisches Training verbessert kognitive Funktionen nicht über Zeit/Remissionseffekte hinaus.

3.2. Abstract

Background: As core feature of schizophrenia cognitive impairment is target of remediation strategies. While deficits respond to cognitive remediation, moderate effect sizes motivate the study of training variants for effect amplification.

Objective: Does targeted neuroplasticity-based training improve cognitive deficits more than nonspecific remediation, (in)dependently of early/chronic stage of illness?

Methods: Cognitive deficits in 59 chronic and 31 firstly admitted patients were determined relative to 25 healthy controls with the MATRICS Consensus Cognitive-Battery. Patients’ performance was assessed before, after two 4-weeks of two targeted neuroplasticity-based training protocols or treatment-as-usual, and at 4-months follow-up.

Results: Performance improved across assessments independently of intervention type, phase of illness, or symptom remission test, though not reaching normal levels.
Conclusion: Short-term course of cognitive deficit improvement is independent of treatment variant and phase of illness. Factors augmenting remediation effects beyond targeting function and neuroplasticity-based learning remain to be scrutinized.
3.3. Theoretischer Hintergrund


Verschiedene Varianten kognitiver Rehabilitation (remediation) wurden untersucht, um diese kognitiven Einschränkungen zu verbessern. Zwar werden übereinstimmend positive Effekte verschiedener Programme bei chronischen (Meta-Analysen McGurk et al., 2007; Wykes et al., 2011; siehe auch Grynszpan et al., 2011; Hodge et al., 2010) und ersterkrankten (Bechdolf et al., 2012; Barlati et al., 2013; Fisher et al., 2014) Patienten (Fußnote 5) berichtet. Effekte werden allerdings z.T. als kurzfristig (Pfammatter et al., 2006; Trapp et al., 2013) eingeschätzt, auch im Vergleich zu Effekten Kognitiver Verhaltenstherapie (z.B. Sarin et al., 2011). Auch werden Effektstärken oft als unbefriedigend gering bis moderat bezeichnet (z.B. Keefe et al., 2012), und nicht als effizienter eingestuft als andere psychologische Therapien wie dem Training sozialer Fertigkeiten, Psychoedukation, Kognitive Verhaltenstherapie (Zusammenfassung Pfammatter et al., 2006), dem Integrierten Psychologischen Therapieprogramm (IPT; z.B. Roder et al., 2011) oder Metakognitivem Training (Moritz et al., 2014). Diese Einschätzung mag zur Weiterentwicklung von Trainingsverfahren angeregt haben, um cognitive Funktionstüchtigkeit stärker und nachhaltiger zu verbessern. Neben klinischen und methodischen Einflüssen wird die spezifische Gestaltung der Intervention als Faktor diskutiert, der das Ausmaß von Behandlungseffekten moduliert (Keefe et al., 2013). So ergab z.B. der Vergleich spezifischer Trainings (Fisher et al., 2013; Merzenich et al., 2014; Rass et al., 2012; Sartory et al., 2006) mit breiter gefächernten (Geibel-Jacobs & Olbrich, 1998) oder durch an-

on zu erwarten, könnte aus Befunden progredienter struktureller Veränderungen (z.B. Asami et al., 2012; Cannon et al., 2014) oder langfristiger Wirkung von insbesondere sedierenden Neuroleptika (Moritz et al., 2013) spekuliert werden, dass ersterkrankte Patienten noch größeres Veränderungspotential und bessere Aktivierbarkeit von Ressourcen zeigen als chronisch Erkrankte. Mit dem Ziel der Hypothesengenerierung verglich die vorliegende Studie daher eine Stichprobe chronisch schizophren Erkrankter und eine Stichprobe ersthospitalisi-
sierter Patienten.

3.4. Methoden

märdiagnose paranoid-halluzinatorische Schizophrenie (F20.0), acht Patienten mit schizoaffektiver Störung (F25.0), vier Patienten erhielten andere Diagnosen aus dem F20 Spektrum. In der Gruppe der ersthospitalisierten Patienten erhielten 21 die Diagnose F20.0, vier die Diagnose F25.0 und sechs die Diagnose einer akuten psychotischen Störung (F23). Beide Patientengruppen unterschieden sich nicht in Geschlechterverteilung oder Schulbildung, die ersthospitalisierten Patienten waren jedoch im Durchschnitt jünger als die chronischen Patienten ($F_{1,88} = 2.58, p < .01$; siehe auch Tabelle 3a). Die ersthospitalisierten Patienten waren vor ihrer Aufnahme nicht neuroleptisch mediziert, Neuroleptika wurden jedoch kurz nach der Aufnahme angesetzt. Entsprechend lag das Chlorpromazin-Äquivalent (CPZ) in der Gruppe der ersthospitalisierten Patienten nur leicht unter dem der chronisch Behandelten ($F_{1,87} = 3.84, p < .1$).
| Demographische Information, klinische Daten und kognitive Variablen der gesamten Stichprobe zu t1. |

<table>
<thead>
<tr>
<th></th>
<th>Schizophrenie Patienten</th>
<th>Kontrollpersonen</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Chronisch (n = 59)</td>
<td>Ersthospitalisiert (n = 31)</td>
</tr>
<tr>
<td>Alter M (SD)</td>
<td>36.9 (9.2)</td>
<td>22.4 (4.1)</td>
</tr>
<tr>
<td>Geschlecht m/w</td>
<td>40/19</td>
<td>24/7</td>
</tr>
<tr>
<td>Bildungsjahre M (SD)</td>
<td>11.2 (1.7)</td>
<td>10.5 (1.7)</td>
</tr>
<tr>
<td>IQ M (SD)</td>
<td>106 (15.9)</td>
<td>102.1 (13.2)</td>
</tr>
<tr>
<td>PANSS-P M (SD)</td>
<td>16.1 (7.7)</td>
<td>16.4 (4.1)</td>
</tr>
<tr>
<td>PANSS-N M (SD)</td>
<td>18.6 (6.3)</td>
<td>17.7 (6.8)</td>
</tr>
<tr>
<td>PANSS-G M (SD)</td>
<td>35.1 (7.7)</td>
<td>35.9 (8.8)</td>
</tr>
<tr>
<td>GAF M (SD)</td>
<td>43.4 (12.9)</td>
<td>49.5 (12.7)</td>
</tr>
<tr>
<td>CPZ M (SD)</td>
<td>614.7 (409.9)</td>
<td>440 (368)</td>
</tr>
<tr>
<td>MCCB Skala M (SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verarbeitungsgeschwindigkeit</td>
<td>41.4 (10.7)</td>
<td>38.2 (11.9)</td>
</tr>
<tr>
<td>Aufmerksamkeit</td>
<td>36.4 (10.6)</td>
<td>37.3 (12.5)</td>
</tr>
<tr>
<td>Arbeitsgedächtnis</td>
<td>47.5 (10.6)</td>
<td>45.7 (10.8)</td>
</tr>
<tr>
<td>Verbales Lernen</td>
<td>46.7 (10.3)</td>
<td>47.5 (10.8)</td>
</tr>
<tr>
<td>Visuelles Lernen</td>
<td>43.3 (13.7)</td>
<td>40.3 (12.3)</td>
</tr>
<tr>
<td>Schlussfolgerndes Denken</td>
<td>47.4 (10.4)</td>
<td>43.5 (10.7)</td>
</tr>
<tr>
<td>Soziale Intelligenz</td>
<td>39.8 (11.1)</td>
<td>44.4 (9.2)</td>
</tr>
</tbody>
</table>

Anmerkungen: M: Mittelwert, SD: Standardabweichung; PANSS-P: Positivsymptome; PANSS-N: Negativsymptome; PANSS-G: allgemeine Symptome; GAF: Global Assessment of Functioning; CPZ: Chlorpromazinäquivalente.
### Tabelle 3b Kognitive Variablen der Patientenstichprobe zu t2 und t3.

<table>
<thead>
<tr>
<th>Schizophrene Patienten</th>
<th>Chronisch (n = 59)</th>
<th>Ersthospitalisiert (n = 31)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>t2: MCCB Skala M (SD)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verarbeitungsgeschwindigkeit</td>
<td>45.8 (11.8)</td>
<td>44.1 (11.9)</td>
</tr>
<tr>
<td>Aufmerksamkeit</td>
<td>40.3 (11.6)</td>
<td>40.1 (11.1)</td>
</tr>
<tr>
<td>Arbeitsgedächtnis</td>
<td>49.3 (11.1)</td>
<td>50.6 (8.6)</td>
</tr>
<tr>
<td>Verbales Lernen</td>
<td>46.2 (10.3)</td>
<td>49.5 (12.0)</td>
</tr>
<tr>
<td>Visuelles Lernen</td>
<td>48.9 (12.4)</td>
<td>42.9 (11.0)</td>
</tr>
<tr>
<td>Schlussfolgerndes Denken</td>
<td>48.2 (8.9)</td>
<td>45.1 (8.4)</td>
</tr>
<tr>
<td>Soziale Intelligenz</td>
<td>40.8 (10.7)</td>
<td>47.5 (10.4)</td>
</tr>
<tr>
<td><strong>t3: MCCB Skala M (SD)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verarbeitungsgeschwindigkeit</td>
<td>48.6 (13.5)</td>
<td>45.1 (11.8)</td>
</tr>
<tr>
<td>Aufmerksamkeit</td>
<td>43.2 (11.0)</td>
<td>42.8 (9.7)</td>
</tr>
<tr>
<td>Arbeitsgedächtnis</td>
<td>52.8 (10.5)</td>
<td>53.6 (8.9)</td>
</tr>
<tr>
<td>Verbales Lernen</td>
<td>51.8 (11.5)</td>
<td>55.0 (9.5)</td>
</tr>
<tr>
<td>Visuelles Lernen</td>
<td>47.7 (13.1)</td>
<td>46.8 (8.1)</td>
</tr>
<tr>
<td>Schlussfolgerndes Denken</td>
<td>49.7 (10.2)</td>
<td>46.2 (9.0)</td>
</tr>
<tr>
<td>Soziale Intelligenz</td>
<td>42.8 (11.1)</td>
<td>46.1 (10.4)</td>
</tr>
</tbody>
</table>

*Anmerkungen:* M: Mittelwert, SD: Standardabweichung; t2: nach 4-wöchiger Intervention; t3: Katamneseuntersuchung.
### Tabelle 3c Demographische Information und klinische Daten von Teilnehmern an der Katamnesemessung und Patienten, die nicht zur Katamnesemessung gewonnen werden konnten.

<table>
<thead>
<tr>
<th>Schizophrenie Patienten</th>
<th>Katamnese Teilnehmer</th>
<th>Nichtteilnehmer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 64)</td>
<td>(n = 26)</td>
</tr>
<tr>
<td>Alter M (SD)</td>
<td>31.5 (10.8)</td>
<td>32.9 (9.5)</td>
</tr>
<tr>
<td>Geschlecht m/w</td>
<td>44/20</td>
<td>20/6</td>
</tr>
<tr>
<td>Bildungsjahre M (SD)</td>
<td>11.1 (1.7)</td>
<td>10.8 (1.9)</td>
</tr>
<tr>
<td>IQ M (SD)</td>
<td>105 (16.2)</td>
<td>104 (12.3)</td>
</tr>
<tr>
<td>PANSS-P M (SD)</td>
<td>15.1 (4.7)</td>
<td>18.9 (9.7)</td>
</tr>
<tr>
<td>PANSS-N M (SD)</td>
<td>17.6 (6.4)</td>
<td>20.1 (6.3)</td>
</tr>
<tr>
<td>PANSS-G M (SD)</td>
<td>34.8 (7.9)</td>
<td>36.9 (8.3)</td>
</tr>
<tr>
<td>GAF M (SD)</td>
<td>46.3 (13.7)</td>
<td>43.5 (12.3)</td>
</tr>
<tr>
<td>CPZ M (SD)</td>
<td>539 (404)</td>
<td>600 (401)</td>
</tr>
</tbody>
</table>

*Anmerkungen: siehe Tabelle 3a.*


**Studienablauf:** Die Studie wurde von der Ethikkommission der Universität Konstanz genehmigt und als klinische Studie (Clinical Trial, ClinicalTrials.gov Registration NCT01781000 und FP 16963311) angemeldet. Die Patienten wurden zu drei Zeitpunkten untersucht, vor Beginn (t1) und nach Abschluss (t2) einer vierwöchigen Interventionsphase und nach drei Monaten Katamnese (t3). Kontrollpersonen nahmen nur an t1 teil. Von den 90 Patienten, die zu t1 und t2 untersucht wurden, konnten 64 für die Katamneseuntersuchung gewonnen werden.
(siehe Abbildung 7 und Tabelle 3c). Vor der ersten Messung wurden die Teilnehmer umfassend über Studienablauf, Freiwilligkeit und Datenschutz informiert und gaben ihr schriftliches Einverständnis zur Teilnahme an der Studie. Nach jeder Testsitzung erhielten sie ein Entgelt von 10 Euro.

Abbildung 7

Für die Interventionsphase wurden die Teilnehmer randomisiert einer von drei Behandlungsvarianten (Fußnote 6) zugewiesen, entweder einem von zwei spezifischen kognitiven Trainings oder dem Standardprogramm der jeweiligen Station (treatment as usual, TAU).
Dabei wurden chronisch erkrankte Patienten entweder einem von zwei spezifischen Trainings (s.u.) oder TAU zugewiesen, während ersthospitalisierte Patienten nur an einer Variante oder an TAU teilnahmen (Fußnote 7). Die spezifischen Trainingsvarianten waren identisch in Bezug auf Computer-gestütztes Einzeltraining, Intensität (täglich eine Stunde an 20 aufeinander folgenden Werktagen), dynamische Anpassung an das individuelle Leistungsniveau (shaping) und motivierenden Kontext (unmittelbare, hochfrequente Verstärkung durch Rückmeldung und symbolische Belohnung). Ebenso betonten beide Trainings Arbeitsgedächtnisfunktionen, sie unterschieden sich in der Konzentration entweder auf Diskrimination akustisch-verbaler Information oder auf Diskrimination affektiver Gesichtsausdrücke.


Das intern für das Forschungsprojekt entwickelte und unveröffentlichte Training visueller Affektdiskrimination FAT (facial affect training) ist analog zu BFP gestaltet und umfasst pro Sitzung 4 15-minütige Aufgabeneinheiten: zwei Diskriminations-fokussierte Übungen betreffen (1) die Differenzierung von 2 affektiven Gesichtsausdrücken in zwei gleichzeitig präsentierten Gesichtern der Karolinska Direktion Emotional Faces (KDEF) Datenbank (http://www.emotionlab.se/resources/kdef, männliche oder weibliche Gesichter, die eine der 6 Standardemotionen nach Ekman & Friesen, Trauer, Freude, Ekel, Furcht, Überraschung, Ärger oder neutralen Ausdruck zeigen); (2) die Identifizierung von 2 Emotionen (aus der gleichen Datenbank), die zu jeweils 50% in dem präsentierten Gesicht kombiniert sind. Zwei Gedächtnis-fokussierte Aufgaben beinhalten (3) die Wiedergabe der Sequenz, mit der


**Messinstrumente:** Der klinische Status wurde mittels der PANSS (Positive and Negative Syndrome Scale; Kay et al., 1987) und der DSM-IV Skala zum globalen Funktionsniveau (GAF) erfasst. Mit der PANSS schätzen die betreuenden Psychiater die Symptomausprägung in der vergangenen Woche in den Bereichen Positivsymptomatik (PANSS-P), Negativsymptomatik (PANSS-N) und allgemeine kognitiv-affektive Symptomatik (PANSS-G) anhand von 7 Symptomen pro Skala (bzw. 14 für PANSS-G) ein. Reliabilität, Stabilität und Konstrukt-validität gelten als gut (Kay et al., 1987). Die Beurteilung des globalen Funktionsniveaus erfolgte anhand der DSM-IV Achse V, auf der Funktionsbeeinträchtigungen im psychischen, sozialen und beruflichen Bereich auf einem Kontinuum zwischen 10 (‘ständige Gefahr, sich oder andere schwer zu verletzen....’) und 100 (’hervorragende Leistungsfähigkeit in einem breiten Spektrum von Aktivitäten...’) kodiert sind.

Das kognitive Leistungsprofil wurde mittels der MCCB (MATRICS Consensus Cognitive Battery; deutsche Übersetzung 2006/2009 (Regents of the University of California, 2006) des MATRICS (Measurement and Treatment Research in Cognition in Schizophrenia) Konsorti-
ums (Nuechterlein & Green, 2006; Nuechterlein et al., 2008) erfasst. Die professionelle deutsche Übersetzung erfolgte im Auftrag des MATRICS Consortium und beinhaltet mehrere vorwärts- sowie zwei Rückwärtsübersetzungen, mehrere Überarbeitungsstufen sowie Feldtestungen von Muttersprachlern.


**Auswertung:** Im ersten Schritt wurden Unterschiede im kognitiven Leistungsprofil zwischen Patienten vor Intervention (n = 90 zu t) und einer Kontrollgruppe (n = 25) geprüft. Hierzu diente eine ANOVA mit dem Zwischensubjektfaktor Diagnose (Patienten/ Kontrollen) und dem Innersubjektfaktor Skala (7 MCCB Skalen). Potentielle Unterschiede zwischen chronischen und ersthospitalisierten Patienten wurden in einer post-hoc ANOVA mit dem Zwischensubjektfaktor Patientengruppe und dem Innersubjektfaktor Skala geprüft.

Da für die Beurteilung von Effekten des Interventionstypus (spezifisches Training oder TAU) auf kognitive Defizite zwei Studien mit teilweise überlappenden Stichproben integriert wurden (Fußnote 7), lag kein ausgewogenes 2 (Gruppen) x 3 (Interventionsart) x Zeit (t-t) Design vor. Entsprechend wurden zu beiden Fragestellungen (Einfluss des Interventionstypus und Einfluss des Krankheitsstadiums auf Interventionseffekte) zwei getrennte varianzanalyti-

3.5. Ergebnisse

Kognitive Defizite bei schizophren Erkrankten vor Intervention wurden über den Vergleich der MCCB Werte zu t1 mit denen der Kontrollgruppe mittels 2 x 7 ANOVA (Diagnose x MCCB-Skalen) verifiziert. Im Vergleich zu Kontrollpersonen zeigten Patienten im Mittel in allen kognitiven Bereichen geringere Testleistungen (Tabellen 3a und 4, Abbildung 8). Effektstärken wiesen für alle Skalen deutliche Unterschiede auf (Hedges’ \( g \) 0.74 – 1.72). Eine Interaktion Diagnose x Skala resultierte aus stärkeren Defiziten bei schizophren Erkrankten in den Bereichen Verarbeitungsgeschwindigkeit, Arbeitsgedächtnis und verbales Lernen.

Innerhalb der Patientenstichprobe unterschieden sich chronische und ersthospitalisierte Patienten nur im Bereich der sozialen Intelligenz deutlich voneinander (Hedges’ \( g \) = 0.5). Weder der Haupteffekt Patientengruppe noch die Interaktion Patientengruppe x Skala erreichte Signifikanz (siehe Tabelle 4). Auch im IQ unterschieden sich die Patientengruppen nicht. IQ und Testleistung korrelierten (ohne signifikanten Unterschied zwischen den Patientengruppen) sowohl mit dem aus allen sieben Skalen berechneten globalen Testleistungs-
wert \((r = .47, p < .01)\) als auch mit einzelnen Leistungsbereichen \((r = .27 – .42, p < .01)\), ausgenommen den Bereichen Schlussfolgerndes Denken und Soziale Intelligenz.

\[\text{Tabelle 4} \quad \text{Kognitive Testleistung zu } t_1.\]

<table>
<thead>
<tr>
<th></th>
<th>Diagnose</th>
<th>Patientengruppe</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(SZ (n = 90))</td>
<td>Chronisch ((n = 59))</td>
</tr>
<tr>
<td></td>
<td>(KG (n = 25))</td>
<td>Ersthospitalisiert ((n = 31))</td>
</tr>
<tr>
<td><strong>ANOVA EFFEKTE</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnose/Patientengruppe</td>
<td>(F_{1,113} = 69.6^{**})</td>
<td>(n. \ s.)</td>
</tr>
<tr>
<td>MCCB Skala</td>
<td>(F_{5,569} = 16.6^{**})</td>
<td>(F_{5,447} = 13.4^{**})</td>
</tr>
<tr>
<td>MCCB Skala (\times)</td>
<td>(F_{5,569} = 3.4^{**})</td>
<td>(F_{5,447} = 2.4^{1})</td>
</tr>
<tr>
<td><strong>POST HOC EFFEKTE</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verarbeitungsgeschwindigkeit</td>
<td>(t_{113} = -7.7^{**})</td>
<td>(n. \ s.)</td>
</tr>
<tr>
<td>Aufmerksamkeit</td>
<td>(t_{113} = -3.9^{**})</td>
<td>(n. \ s.)</td>
</tr>
<tr>
<td>Arbeitsgedächtnis</td>
<td>(t_{113} = -5.7^{**})</td>
<td>(n. \ s.)</td>
</tr>
<tr>
<td>Verbales Lernen</td>
<td>(t_{113} = -5.7^{**})</td>
<td>(n. \ s.)</td>
</tr>
<tr>
<td>Visuelles Lernen</td>
<td>(t_{113} = -4.6^{**})</td>
<td>(n. \ s.)</td>
</tr>
<tr>
<td>Schlussfolgerndes Denken</td>
<td>(t_{113} = -3.3^{**})</td>
<td>(n. \ s.)</td>
</tr>
<tr>
<td>Soziale Intelligenz</td>
<td>(t_{113} = -4.8^{**})</td>
<td>(t_{88} = -2.1^{*})</td>
</tr>
</tbody>
</table>

Anmerkungen: * \(p < .05\), ** \(p < .01\), \(^1\) \(p < .1\). SZ = Schizophrenie Patienten; KG = Gesunde Kontrollgruppe.
Abbildung 8

(A) Mittlere Leistung (T-Werte, M ± SD) für die MCCB-Skalen Verarbeitungsgeschwindigkeit (VGS), Aufmerksamkeit (AM), Arbeitsgedächtnis (AG) Verbales Lernen (Verbl), Visuelles Lernen (VisL), Schlussfolgerndes Denken und Problemlösen (SD), Soziale Intelligenz (SI) getrennt für Schizophrenie Patienten (SZ) und gesunde Kontrollpersonen (KG).

(B) Effektstärken (Hedges’ g) für den Unterschied zwischen Schizophrenie Patienten und gesunden Kontrollpersonen für jede MCCB-Skala (Abkürzungen wie in Abbildung 8 (A)).
Abbildung 9
Effektstärken (Hedges’ g) für die zeitliche Veränderung innerhalb der Patientenstichprobe zwischen t1 (vor der Intervention) und t2 (nach vierwöchiger Intervention) und zwischen t2 und t3 (drei Monate nach Intervention) für jede MCCB-Skala (Abkürzungen wie in Abbildung 8 (A)).

Zum zweiten Messzeitpunkt nach Ende der Interventionsphase zeigten Patienten (über die gesamte Stichprobe von n = 90 Patienten gemittelt) verbesserte Testleistungen (Zeit t1 – t2, $F_{1,114} = 34.63, p < .001$; vergleiche auch Tabelle 3a und 3b). Wie auch Effektstärken in Abbildung 9 illustrieren, fiel der Leistungszuwachs für die einzelnen MCCB Skalen unterschiedlich deutlich aus (Zeit x Skala, $F_{6,684} = 3.39, p < .05$; Skala, $F_{6,684} = 22.34, p < .01$). Post-hoc-Vergleiche bestätigten signifikante Verbesserungen in den Skalen Verarbeitungsgeschwindigkeit ($t_{89} = 5.9, p < .01$), Aufmerksamkeit ($t_{89} = 4.1, p < .01$), Arbeitsgedächtnis ($t_{89} = 3.5, p < .01$), visuelles Lernen ($t_{89} = 3.3, p < .01$), und soziale Intelligenz ($t_{89} = 2.1, p < .05$). Wie Abbildung 9 ebenfalls verdeutlicht, nahm die Leistungssteigerung in den Skalen Arbeitsgedächtnis und verbales Lernen in der Katamnesephase weiter zu (Zeit t2 – t3 x Skala, $F_{6,372} = 2.43, p < .05$; Zeit, $F_{1,62} = 8.00, p < .01$; Skala, $F_{6,372} = 12.09, p < .01$). Ein explorativer Vergleich der Testleistungen nach Intervention (t2) und zum Katamnesezeitpunkt (t3) mit Testleistungen, wie sie für die Normalpopulation aus den Testleistungen der vorliegenden Kontrollgruppe zu t1 geschlossen werden, ergab weiterhin signifikante Gruppenunterschiede (Patienten t2 vs. Kontrollgruppe t1: $F_{1,113} = 45.21, p < .001$; Patienten t3 vs. Kontrollgruppe t1: $F_{1,80} = 20.91, p < .001$).
Der Einfluss spezifischer Trainings gegenüber dem stationären Standardprogramm wurde für die Stichprobe chronischer Patienten mittels ANOVA mit Messwiederholung mit dem Innersubjektfaktor Zeit (t1 - t2) und dem Zwischensubjekt-Faktor Interventionstypus (BFP, FAT, TAU) geprüft. Dabei ergaben sich keine unterschiedlichen Leistungsverbesserungen nach den spezifischen Trainings BFP und FAT gegenüber TAU (siehe Tabelle 5a), d.h. die schwach signifikante Dreifach-Interaktion (Intervention x Zeit x Skala, F6,342 = 2.17, p < .05) resultierte aus signifikanter Verbesserung beider Trainingsgruppen gegenüber TAU in der MCCB Skala Schlussfolgerndes Denken. Gezielte Einzelvergleiche bestätigten nicht die gerichteten Hypothesen zu trainingsspezifischen Verbesserungen in Arbeitsgedächtnis, verbalem oder visuellem Lernen und Sozialer Intelligenz (Interaktion Training x Zeit für Skalen Arbeitsgedächtnis, verbales Lernen, visuelles Lernen, soziale Intelligenz n.s.).

Die Stabilität der Leistungsverbesserung wurde für die Stichprobe von n = 42 chronischen Patienten, die für die Katamnesemessung gewonnen werden konnte, anhand einer ANOVA mit dem Innersubjektfaktor Zeit (t2 – t3) geprüft. Wiederum unabhängig vom Interventionstypus (spezifische Trainings oder TAU) ergab sich Stabilität, d.h. keine Unterschiede im Leistungsniveau zwischen t2 und t3. Unabhängig vom Interventionstypus verbesserte sich die Leistung im Verbalen Lernen (F1,47 = 16.59, p < .01).
Tabelle 5a Kognitive Testleistungen (Innersubjektfaktor MCCB-Skala, 7-stufig) zwischen Messzeitpunkten vor und nach Interventionsphase (t1 – t2) sowie zwischen Intervention und Katamnese (t2 – t3) (Innersubjektfaktor Zeit, jeweils 2-stufig) bei chronischen Patienten in Abhängigkeit von spezifischen Trainings und TAU.

<table>
<thead>
<tr>
<th>Intervention (spez. Trainings, TAU)</th>
<th>t1-t2 ( n = 59 )</th>
<th>t2-t3 ( n = 42 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zeit</td>
<td>n. s.</td>
<td>n. s.</td>
</tr>
<tr>
<td>Zeit x Intervention</td>
<td>( F_{1,57} = 19.2^{**} )</td>
<td>( F_{1,40} = 3.5^1 )</td>
</tr>
<tr>
<td>Skala</td>
<td>n. s.</td>
<td>n. s.</td>
</tr>
<tr>
<td>Skala x Zeit</td>
<td>( F_{6,342} = 12.1^{**} )</td>
<td>( F_{6,240} = 7.58^{**} )</td>
</tr>
<tr>
<td>Skala x Intervention</td>
<td>( F_{6,342} = 3.5^{**} )</td>
<td>( F_{6,240} = 2.8^{*} )</td>
</tr>
<tr>
<td>Skala x Zeit x Intervention</td>
<td>n. s.</td>
<td>( F_{6,240} = 2.5^{*} )</td>
</tr>
<tr>
<td>Training (BFP, FAT, TAU)</td>
<td>n. s.</td>
<td>n. s.</td>
</tr>
<tr>
<td>Zeit</td>
<td>n. s.</td>
<td>n. s.</td>
</tr>
<tr>
<td>Zeit x Training</td>
<td>( F_{1,56} = 23.4^{**} )</td>
<td>n. s.</td>
</tr>
<tr>
<td>Skala</td>
<td>n. s.</td>
<td>n. s.</td>
</tr>
<tr>
<td>Skala x Zeit</td>
<td>( F_{6,336} = 13.8^{**} )</td>
<td>( F_{6,234} = 9.0^{**} )</td>
</tr>
<tr>
<td>Skala x Training</td>
<td>( F_{6,336} = 3.8^{*} )</td>
<td>( F_{6,234} = 3.35^{**} )</td>
</tr>
<tr>
<td>Skala x Zeit x Training</td>
<td>n. s.</td>
<td>n. s.</td>
</tr>
<tr>
<td>Training (BFP, FAT)</td>
<td>n. s.</td>
<td>n. s.</td>
</tr>
<tr>
<td>Zeit</td>
<td>n. s.</td>
<td>n. s.</td>
</tr>
<tr>
<td>Zeit x Training</td>
<td>( F_{1,30} = 19.2^{**} )</td>
<td>n. s.</td>
</tr>
<tr>
<td>Skala</td>
<td>n. s.</td>
<td>n. s.</td>
</tr>
<tr>
<td>Skala x Zeit</td>
<td>( F_{6,216} = 10.0^{**} )</td>
<td>( F_{6,162} = 7.9^{**} )</td>
</tr>
<tr>
<td>Skala x Training</td>
<td>( F_{6,216} = 3.5^{*} )</td>
<td>( F_{6,162} = 2.4^{*} )</td>
</tr>
<tr>
<td>Skala x Zeit x Training</td>
<td>n. s.</td>
<td>n. s.</td>
</tr>
</tbody>
</table>

Anmerkungen: Zwischengruppenfaktor Intervention: 2-stufiger Vergleich spezifischer Trainings mit unspezifischem TAU. Zwischengruppenfaktor Training: 3-stufiger Vergleich der zwei spezifischen Trainings, BFP und FAT, und TAU. Zwischengruppenfaktor Training: 2-stufiger Vergleich von BFP und FAT. * \( p < .05 \). ** \( p < .01 \). \(^{1}\) \( t < .1 \).
Tabelle 5b Kognitive Testleistungen (Innersubjektfaktor MCCB-Skala, 7-stufig) zwischen Messzeitpunkten (Innersubjektfaktor Zeit, jeweils 2-stufig) vor und nach Interventionsphase (t1 – t2) sowie zwischen Intervention und Katamnese (t2 – t3) bei chronischen und ersthospitalisierten Patienten (Zwischensubjektfaktor Patienten-gruppe) in Abhängigkeit von BFP und TAU (Zwischengruppenfaktor Intervention).

<table>
<thead>
<tr>
<th></th>
<th>t1-t2 n = 70</th>
<th>t2-t3 n = 50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patientengruppe (chronisch, ersthospital.)</td>
<td>n. s.</td>
<td>n. s.</td>
</tr>
<tr>
<td>Intervention (BFP, TAU)</td>
<td>n. s.</td>
<td>n. s.</td>
</tr>
<tr>
<td>Zeit</td>
<td>$F_{1,66} = 23.2^{**}$</td>
<td>$F_{1,46} = 12.8^{**}$</td>
</tr>
<tr>
<td>Zeit x Intervention</td>
<td>n. s.</td>
<td>n. s.</td>
</tr>
<tr>
<td>Zeit x Patientengruppe</td>
<td>n. s.</td>
<td>n. s.</td>
</tr>
<tr>
<td>Skala</td>
<td>$F_{6,396} = 10.7^{**}$</td>
<td>$F_{6,276} = 8.7^{**}$</td>
</tr>
<tr>
<td>Skala x Zeit</td>
<td>$F_{6,396} = 2.9^{**}$</td>
<td>$F_{6,234} = 2.1^{*}$</td>
</tr>
<tr>
<td>Skala x Patientengruppe</td>
<td>n. s.</td>
<td>n. s.</td>
</tr>
<tr>
<td>Skala x Zeit x Intervention</td>
<td>n. s.</td>
<td>n. s.</td>
</tr>
<tr>
<td>Patientengruppe x Intervention x Zeit x Skala</td>
<td>n. s.</td>
<td>n. s.</td>
</tr>
</tbody>
</table>


Angesichts der relativ hohen Zahl von Patienten, die nicht mehr für die Katamnese gewonnen werden konnten, wurden explorativ untersucht, inwieweit sich demographische, klinische und testpsychologische Kennwerte zwischen teilnehmenden Patienten (n = 64) und Nichtteilnehmern (n = 26) unterschieden. Während sich keine Unterschiede in demographischen Variablen fanden (siehe Tabelle 3c), zeigten Nichtteilnehmer bereits zu t1 mehr Defizite in Arbeitsgedächtnis- ($t_{88} = 2.2, p < .05$) und Aufmerksamkeit ($t_{88} = 2.8, p < .05$) sowie stärker ausgeprägte Positivsymptomatik ($t_{88} = 2.28, p < .05$).

Der Einfluss des Krankheitsstadiums (ersthospitalisiert versus chronisch) auf Trainingseffekte wurde für n = 31 ersthospitalisierte und n =39 chronische Patienten, die jeweils entweder BFP oder TAU zugewiesen worden waren, über ANOVAs mit Messwiederholung mit dem Innersubjektfaktor Zeit (t1 - t2) und den Zwischensubjekt-faktoren Patientengruppe (ersthospitalisiert vs. chronisch) und Intervention (BFP vs. TAU) geprüft. Weder Haupeffekte (Patientengruppe, Intervention) noch Wechselwirkungen mit dem Faktor Zeit (Tabelle 5b) erreichten Signifikanz, die auf eine Modulation der Leistungsverbesserungen durch das Krankheitsstadium hinwiesen. Dies galt für Verbesserungen nach der Interventionsphase (t1
– t2) ebenso wie für die Katamnesephase (t2 – t3). Ein Einfluss der Symptomatik auf Ausprägung und Modulierbarkeit kognitiver Defizite wurde korrelations- und regressionsanalytisch geprüft. Sowohl Symptomatik als auch das globale Funktionsniveau verbesserten sich im Verlauf der Behandlung/Remission (Zeit: PANSS-P, $F_{1,86} = 23.3$, $p < .001$; PANSS-N, $F_{1,86} = 4.8$, $p < .05$; PANSS-G, $F_{1,86} = 14.1$, $p < .001$; GAF: $F_{1,84} = 63.0$, $p < .001$). Wie aus Tabelle 6 ersichtlich wird, varierte insbesondere Negativsymptomatik vor (t1) und nach Intervention (t2) mit Verarbeitungsgeschwindigkeit und verbalem Lernen.

**Tabelle 6** Korrelationen der MCCB-Skalen mit der klinischen Symptomatik.

<table>
<thead>
<tr>
<th>Zeitpunkt und MCCB-Skala</th>
<th>Patienten gesamt ($n = 90$)</th>
<th>Ersthospitalisierte Pat. ($n = 31$)</th>
<th>Chronische Pat. ($n = 59$)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PANSS</td>
<td>PANSS</td>
<td>PANSS</td>
</tr>
<tr>
<td>t1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>VGS</td>
<td>-.33**</td>
<td>-.68**</td>
</tr>
<tr>
<td></td>
<td>VerbL</td>
<td>-.49**</td>
<td></td>
</tr>
<tr>
<td>t2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>VGS</td>
<td>-.39**</td>
<td>-.57**</td>
</tr>
<tr>
<td></td>
<td>VerbL</td>
<td>-.31** - .43**</td>
<td>-.48** -.60**</td>
</tr>
<tr>
<td></td>
<td>SI</td>
<td>-.25*</td>
<td>.45**</td>
</tr>
</tbody>
</table>

*Anmerkungen:* Bonferroni-Holm korrigierte Korrelationen; * $p < .05$. ** $p < .01$. VGS: Verarbeitungsgeschwindigkeit; VerbL: Verbales Lernen; SI: Soziale Intelligenz; P: Positivsymptome; N: Negativsymptome; G: Generelle Symptome.

Zum Zeitpunkt der Katamnese ergaben sich keine überzufälligen Zusammenhänge mit der Testleistung bzw. Leistungsverbesserung. Die Testleistung zu t2 ließ sich regressionsanalytisch nicht aus der Symptomausprägung bzw. -verbesserung aufklären bzw. vorhersagen, und Testleistungen bzw. deren Verbesserungen (t1-t2) trugen nicht zur Varianzaufklärung des globalen Funktionsniveaus (GAF) zu t2 bei. Das globale Funktionsniveau zu t2 ließ sich moderat ($R^2 = .29$, $p < .01$) aus Verbesserungen der Symptomatik (PANSS-G t1-t2), dem Erkrankungsstadium (chronisch, ersthospitalisiert) und verbaler Leistungsfähigkeit zu t1 vorhersagen. Zu keinem Messzeitpunkt ergaben sich Zusammenhänge zwischen Testleistungen und Medikation (gemessen anhand von CPZ Äquivalenten).

**3.6. Diskussion**

Weiterentwicklungen im Bereich kognitiver Remediation dienen unter anderem dem Ziel, die bisher oft als unbefriedigend bezeichneten Effekte auf kognitive Defizite bei schizophrenen...

Verschiedene Erklärungen für die trainings-unabhängigen Verbesserungen über die Zeit liegen nahe:

Das stationäre Angebot (TAU) ähnelt der Kombination von einzelnen, als effektiv beschriebenen Maßnahmen wie KVT (z.B. Klingberg et al., 2011) und Psychoedukation (Bechdolf et al., 2005; Pitschel-Walz et al., 2013) und aktivierte damit sozial-kognitive Funktionen bereits soweit, dass spezifische Trainingsprogramme nicht zu darüber hinaus gehender, statistisch signifikanter weiterer Funktionserholung führte. Dies stützt Befunde ähnlicher Wirksamkeit breit gefächerten und spezifischer Remediationsprogramme (Wykes et al., 201; Bechdolf et al., 2012; Kurtz & Richardson, 2012; Sánchez et al., 2014; Wölwer & Frommann, 2011), könnte aber auch auf allgemeine Remission über die Zeit hindeuten (Braw et al., 2012), die in der vorliegenden Studie nicht auspartialisert werden konnten. Auch für BFP wurden deutlichere Effekte bei Kombination mit sozial-kognitivem Training berichtet (Hooker et al., 2013; Sacks et al., 2013). Ein singuläres spezifisches Training reicht möglicherweise nicht aus, um kognitive Defizite über den Effekt allgemeiner Remission hinaus zu reduzieren.

Die in den spezifischen Trainings gestalteten Bedingungen zur Förderung kortikaler Reorganisation und das gezielte Training vermuteter Basisfunktionen wie Informationsdiskrimination, -enkodierung und -speicherung (Merzenich. 2013) wirkten sich nicht, wie erwartet, auf höhere kognitive Funktionen aus, die sich in kognitiven Testleistungen abbilden. Ebenso denkbar ist, dass die spezifischen Trainings kortikale Grundlagen kognitiver Defizite nicht ausreichend berücksichtigt: BFP orientiert sich u.a. an der Annahme eines bei Schizophrenien gestörten neuronalen Signal-Rausch-Verhältnisses (Merzenich et al., 2014). Es ist eben-
so denkbar, dass andere neuronale Dysfunktionen (z.B. Uhlhaas, 2011, 2013; Haenschel et al., 2009; Rubinov & Bullmore, 2013), auf die die gewählten spezifischen Trainings nicht ausreichend zugeschnitten waren, zu kognitiven Defiziten beitragen.


Es erscheint möglich, dass die MCCB spezifisch trainierten Funktionen unzureichend abbildet. Die MCCB wurde vom MATRICS Konsortium entwickelt, um zentrale kognitive Defizite schizophren Erkrankter zu erfassen (Keefe et al., 2011). Entsprechend wurde erwartet, dass die gezielt auf Arbeitsgedächtnis, verbale und visuell-affektive Diskrimination konzentrierten Trainings sich auf Leistungen in den entsprechenden MCCB-Tests zu Arbeitsgedächtnis, verbalem und visuellem Lernen oder sozialer Intelligenz auswirkten. Dies ließ sich nicht bestätigen. Im Verlauf des Affektdiskriminationstrainings (FAT) zeigten sich deutliche Verbesserungen in funktionsnahen Leistungsparametern (Popova et al., 2014). Eine Korrelation zwischen diesem Leistungszuwachs und den MCCB-Skalen Visuelles Lernen oder Soziale Kognition ergab sich dagegen nicht. Insbesondere der sozial-kognitive Funktionen repräsentierende MCCB-Test (MSCEIT, Mayer-Salovey-Caruso Emotional Intelligence Test; Mayer-Salovey et al., 2003; Dawson et al., 2012), erfasst eher komplexe Funktionen, die das vorliegende Affektdiskriminationstraining nicht ansprach.

Wiederholt wurde der Einfluss antipsychotischer Medikation auf kognitive (Test)leistungen thematisiert (z.B. Kane, 2011; Moritz et al. 2013), auch wenn kognitive Defizite auch bei unmedizierten Patient/innen bestätigt wurden (Fatouros-Bergman et al., 2014). Insbesondere wurde darauf hingewiesen, dass sedierende und antidopaminerge Wirkungen anti-
psychotischer Medikation die Lernfähigkeit bzw. Motivation behindert (Pessiglione et al., 2006), was sich auf den Effekt von Training auswirken könnte. Andererseits scheint noch unzureichend geklärt, inwieweit pharmakologische Behandlung zur Verbesserung kognitiver Defizite beiträgt (Harvey & McClure, 2006; Harvey, 2009; Keefe et al., 2013; Vingerhoets et al., 2013). In der vorliegenden Studie ließ sich kein Zusammenhang zwischen Medikation und Testleistung oder deren Veränderung über die Zeit dokumentieren. Der Einfluss der Medikation auf Interventionseffekte und Testleistungen kann allerdings nur durch den direkten Vergleich medizierter und unmedizierter Patienten im jeweiligen Trainingsprogramm präzisiert werden. Dies war im vorliegenden klinischen Setting nicht möglich. Der fehlende Unterschied im CPZ zwischen den Gruppen und Testsitzungen erlaubt keinen ausreichenden Rück­schluss auf medikamentös stabile Phasen.


strukturellen Veränderungen mit Behandlungseffekten interagieren. In der vorliegenden Studie ergaben sich keine Unterschiede in der Leistungsverbesserung zwischen ersthospitalisierten und chronisch erkrankten Patienten (siehe auch Fisher et al., 2013 und 2014). In der vorliegenden Studie war die verfügbare Information über das Stadium im Krankheitsverlauf allerdings unzureichend (u.a. fehlende strukturelle Bildgebung), um auf eingeschränktes Erholungs- und Reorganisationspotential bei chronisch schizophren Erkrankten oder höhere Flexibilität desselben bei ersterkrankten Patienten schließen zu können.


Methodische Einschränkungen, die in ähnlicher Weise auch für andere Interventionsstudien im klinischen Setting genannt werden (Keefe et al., 2013), begrenzen Folgerungen aus den vorliegenden Ergebnissen. Trotz der relativ großen Gesamtstichprobe von 90 Patienten blieb die Anzahl Patienten in jedem Interventionsarm zu gering, um deutlichere Effekte abzuschirmen. Ein methodisch angemessenes ausgewogenes Design mit ausreichend großen Subgruppen chronischer und ersthospitalisierter Patienten in jedem Interventionsarm liess sich im gegebenen klinischen Setting nicht umsetzen. Ebenso ließ sich die Medikation (Art und
Stabilität) über die Interventions- und Katamnesephase hinweg im klinischen Setting nicht kontrollieren.

Insgesamt zeigen die Ergebnisse dieser Studie, dass kognitive Defizite bei schizophren Erkrankten nicht stabil bzw. über den Krankheitsverlauf progredient sind. Inwieweit die beobachteten Verbesserungen einen unspezifischen Remissionseffekt reflektieren, der durch gezielte Maßnahmen nicht verstärkt werden kann, oder inwieweit die hier untersuchten Trainingsvarianten nicht ausreichend gestaltet waren, um diese Verstärkung herbei zu führen, bleibt in weiteren Studien zu prüfen.
4. Neuroplasticity-Based Training Modifies Oscillatory Dynamics in First-Episode Schizophrenia Patients

4.1. Abstract

Background: The similarity of cognitive deficits and dysfunctional brain activity between first-episode (FE) and chronic schizophrenia patients suggests that psychopathology is manifest early in the course of illness. Cognitive training impacts cognitive function and functional decline, while the effects on their neuronal underpinnings remain to be substantiated. The present study evaluated training effects in FE on alpha activity as a measure of facilitated neuronal input processing.

Methods: Modulations of 8-12 Hz oscillations in an auditory paired-click task and cognitive test performance (MCCB) were monitored in 35 FE before and after either four weeks of neuroplasticity-based training targeting (TT) auditory-verbal discrimination and memory, or treatment as usual (TAU). Comparison with 25 healthy subjects assessed cognitive deficits and dysfunctional alpha activity before training/TAU.

Results: Prior to intervention, FE did not show the induced alpha power decrease seen in HC. Patients’ alpha power decrease was significantly augmented immediately and three months after targeted training, but not after TAU. Cognitive test performance improved across training and follow-up without a difference between targeted training and TAU.

Conclusion: The impact of targeted training on oscillatory activity indexing neuronal signal differentiation and processing recommends a potential for cortical reorganization in FE for early, intense and targeted intervention.
4.2. Introduction

Cognitive deficits in schizophrenia (Heinrichs, 2004; Heinrichs et al., 2013) are prominent in chronic, FE, high-risk and prodromal states (Carolus et al., 2014; Gopal, 2005; Hafner, 2000; Hafner & Maurer, 2006; Holmen et al., 2010; Mesholam-Gately et al., 2009), are often resistant to neuroleptic treatment (Goff et al., 2011; Harvey, 2009) and are related to an unfavorable course of illness (Dickinson et al., 2010; Grynszpan et al., 2011; McGurk et al., 2007; van der Gaag et al., 2002; Wykes et al., 2011) or poor social and occupational outcome (Green et al., 2012; Nuechterlein et al., 2011). Cognitive remediation treatment (CRT; Gopal, 2005; Singh, 2013), compensatory cognitive training (Mendella et al., 2015) and computerized neuroplasticity-based training (Fisher et al., 2014) are shown to improve cognitive functioning in FE (FE) patients and delay psychotic transition in high-risk patients (A Bechdolf et al., 2012), though evidence of this is still considered insufficient (Barlati et al., 2012). Mild to moderate effect sizes of CRT in chronic and FE patients (Grynszpan et al., 2011; T. Wykes et al., 2011) directed the attention to neural mechanisms of cognitive (dys)function as a target of training and remediation protocols (Kaneko & Keshavan, 2012; Merzenich et al., 2014; Saperstein & Kurtz, 2013; Silverstein & Wilkniss, 2004).

Insights into neuronal mechanisms of perceptual and cognitive processing and their disruption in schizophrenia are expected from oscillatory dynamics, which index temporally structured neuronal signals at the basis of the excitatory/inhibitory balance within and between neuronal networks (Abeles & Gomez-Ramirez, 2014; Buzsáki, 2010; Hanslmayr et al., 2012; Jensen & Mazaheri, 2010). In chronic and FE patients, abnormal oscillatory activity has been reported for lower (theta and alpha; e.g., Abeles & Gomez-Ramirez, 2014; Missonnier et al., 2012) and higher (gamma) frequency bands in particular (e.g., Haenschel et al., 2009; Minzenberg et al., 2010; Ramyead et al., 2014; Symond et al., 2005; Tikka et al., 2014), lower resting state 8-14 Hz (alpha) activity relative to healthy controls, and less stimulus-induced alpha power decrease relative to the pre-stimulus baseline (e.g., Abeles & Gomez-Ramirez, 2014; Carolus et al., 2014; Popov et al., 2011; Sponheim et al., 1994; Wada et al., 1994). As a stimulus-induced alpha power decrease is associated with neural network readiness for information intake and coding (Buzsáki & Watson, 2012; Jensen & Mazaheri, 2010), disrupted alpha power modulation may indicate poor neuronal signal resolution, which is considered as the basis of disrupted perceptual and cognitive processing in schizophrenia (Merzenich et al., 2014; Merzenich, 2013).
Neuroplasticity-based training targeting auditory-verbal learning and memory addresses these neuronal mechanisms of auditory signal differentiation and thereby affects deficits in higher-order verbal learning and memory (Merzenich et al., 2014; Merzenich, 2013). Moreover, deficient neuroplasticity characterizes schizophrenia pathophysiology (Buonanno, 2010; Rosen et al., 2015; Uhlhaas et al., 2008). Evidence of training-driven neuroplasticity and associated changes in functional brain activity inform conditions for training and remediation programs (Elbert & Rockstroh, 2004; Merzenich et al., 2014). Previous studies from our group have demonstrated training effects on abnormal alpha power modulation in chronic patients (Popov et al., 2015, 2012).

The present study sought to demonstrate such effects in FE as indication of (a) early abnormality and (b) the potential functional cortical reorganization early in the course of illness. Effects of neuroplasticity-based targeted training (TT) on induced alpha power modulation and on cognitive test performance (MCCB, Measurement and Treatment Research in Cognition in Schizophrenia; Nuechterlein & Green, 2006) were compared to effects of the unit’s standard ‘treatment-as-usual’ regimen (TAU) with the primary hypotheses: (1) FE who accomplished TT show greater changes in alpha power modulation in the paired-stimulus task than FE undergoing TAU; (2) training-induced changes persist across a three-month follow-up period; and (3) training-induced alpha power modulation varies with improvement of cognitive test performance, in particular with performance in specifically trained cognitive domains such as verbal learning and working memory.

4.3. Methods

Participants: 35 patients meeting ICD criteria for schizophrenia and admitted for inpatient treatment for the first time (defined as first-episode, FE) were recruited from an inpatient unit of the regional center for psychiatry. Diagnosed by experienced senior psychiatrists and psychologists, \( n = 28 \) FE were diagnosed as paranoid-hallucinatory schizophrenia (ICD code F20.0), \( n = 3 \) as schizoaffective disorder (ICD code F25.1), and \( n = 4 \) as acute transient psychosis (ICD code F23). First experiences of positive symptoms were reported 1 to 52 weeks before admission (mean 8.7 weeks). Patients were included if they did not report any history of neurological conditions or disorders, including epilepsy or head trauma with a loss of consciousness. Table 7 summarizes the sample characteristics at study admission. Prior to the first assessment (details below), patients were pseudo-randomly assigned to training (BFP, Brain Fitness Program, Posit Science, San Francisco, USA; description below) or TAU. Re-
recruitment continued until 20 patients per group had accomplished the pre-intervention assessment. After dropouts and early releases during the intervention period had occurred (mainly in the TAU group), data from 20 BFP patients and 15 TAU patients TAU were available for post-intervention assessment. Patient subgroups did not differ in age, gender distribution, years of education or IQ (as assessed using a standard German test for premorbid intelligence; Lehrl, 2005; Table 7).

**Table 7** Demographic information for first episode schizophrenia patients (FE) and healthy comparison participants (HC) at t1 (prior to intervention), as well as clinical variables of FE subgroups assigned to targeted training (BFP) or treatment-as-usual (TAU) at t1.

<table>
<thead>
<tr>
<th></th>
<th>FE (n = 35)</th>
<th>HC (n = 25)</th>
<th>FE vs. HC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age M (SD)</td>
<td>22.4 (3.8)</td>
<td>29.3 (9.5)</td>
<td>(F_{(1,58)} = 15.1, \ p&lt;.01)</td>
</tr>
<tr>
<td>Sex m/f</td>
<td>26/9</td>
<td>13/12</td>
<td>(\text{Chi}^2_{(1)} = 2.3, \ p&gt;.1,\ n.s.)</td>
</tr>
<tr>
<td>Years of Education M (SD)</td>
<td>10.7 (1.8)</td>
<td>12.0 (1.5)</td>
<td>(F_{(1,58)} = 3.6, \ p&gt;.05,\ n.s.)</td>
</tr>
</tbody>
</table>

**Training Groups (pre intervention)**

<table>
<thead>
<tr>
<th></th>
<th>BFP (n = 20)</th>
<th>TAU (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age M (SD)</td>
<td>21.9 (3.1)</td>
<td>22.9 (4.5)</td>
</tr>
<tr>
<td>Sex m/f</td>
<td>14/6</td>
<td>12/3</td>
</tr>
<tr>
<td>Years of Education M (SD)</td>
<td>10.8 (1.9)</td>
<td>10.6 (1.7)</td>
</tr>
<tr>
<td>IQ M (SD)</td>
<td>100 (11.6)</td>
<td>105.1 (14.1)</td>
</tr>
<tr>
<td>PANSS-P M (SD)</td>
<td>16.1 (4.3)</td>
<td>15.9 (4.1)</td>
</tr>
<tr>
<td>PANSS-N M (SD)</td>
<td>17.9 (6.6)</td>
<td>16.7 (7.9)</td>
</tr>
<tr>
<td>PANSS-G M (SD)</td>
<td>35.9 (8.2)</td>
<td>35.9 (10.1)</td>
</tr>
<tr>
<td>GAF M (SD)</td>
<td>48.8 (13.7)</td>
<td>54.7 (12.3)</td>
</tr>
<tr>
<td>CPZ M (SD)</td>
<td>395.0 (261)</td>
<td>441.3 (462)</td>
</tr>
</tbody>
</table>

Notes: first-episode schizophrenia patients; HC: healthy comparison participants; M: Mean, SD: standard deviation; PANSS-P: Positive symptoms; PANSS-N: Negative symptoms; PANSS-G: general symptoms; GAF: DSM-IV scale Global Assessment of Functioning (DSM-IV axis 5); CPZ: Chlorpromazine equivalent; BFP: Brain Fitness Program; TAU: Treatment-as-usual.
Neither pre-intervention clinical status, evaluated using the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987) nor global functioning, evaluated using DSM-IV Axis V-based, GAF score, differed between the BFP and TAU groups. While none of the FE had been treated with neuroleptics prior to admission, all had started neuroleptic medication by the time of the assessment. The chlorpromazine equivalent did not differ between patients assigned to BFP and to TAU.

Pre-intervention neuromagnetic and cognitive measures were compared to those of 25 healthy comparison subjects (HC; see Table 7 for demographic information), overlapping with the sample described in Carolus et al. (2014) and Popov et al. (2015).

**Design and Procedure:** The study was approved by the ethics committee of the University of Konstanz and registered as clinical trial (ClinicalTrials.gov Registration FP 16963311). Participants provided written informed consent prior to the study and received €30 upon completion of each session. The study design comprised three assessments of neuromagnetic activity monitored in the paired-click task, and cognitive performance on the MATRICS Consortium Cognitive Battery (MCCB, Nuechterlein et al., 2008): pre-intervention (t1), after the four-week intervention (post-intervention, t2) and three months after t2 (follow-up, t3).

The BFP protocol implements computer-based exposure, intensity, shaping and a reinforcement algorithm that fosters neuroplasticity (Elbert & Rockstroh, 2004; Merzenich et al., 2014): 20 daily one-hour sessions were scheduled on consecutive work days within a period of four weeks, a computer algorithm providing the individual adjustment of task difficulty as a function of performance and motivating feedback was provided for each task and session. BFP consists of six exercises: judging gradually more difficult distinctions between frequency modulation sweeps of auditory stimuli that increase or decrease in frequency, distinguishing phonemes with synthesized speech, identifying arrays of open and closed syllables in a spatial and temporal context, discriminating tone frequencies, and remembering details of short narratives. TAU comprised participation in the unit’s treatment program of individual and group psychotherapy, physical exercises and social skills training.

**Data collection and analyses:** Prior to magnetoencephalographic (MEG) measurement, individual hearing levels were separately determined for each ear via an adapted method of
limits (Gescheider, 1997). The paired-click task comprised 100 pairs of 3-ms square-wave clicks (S1 - S2) presented with 500-ms onset-to-onset interstimulus intervals and a variable offset to onset interval of 7-9 s. Clicks were presented 60 dB above individual hearing level and delivered via 5-m non-ferromagnetic tubes. No performance task was involved, except that participants were asked to keep their eyes focused on a small fixation point throughout the procedure. The MEG was recorded using a 148-channel magnetometer (MAGNES 2500 WH, 4D Neuroimaging, San Diego, USA) while subjects were in a supine position. Data were continuously recorded with a sampling rate of 678.17 Hz and a bandpass filter of 0.1 to 200 Hz. The subject’s nasion, left and right ear canal, and head shape were digitized using a Polhemus 3Space Fasttrack prior to each session. Before correcting for heart and eye-blink artifacts by means of independent component analysis, trials containing movement artifacts or SQUID jumps were rejected based on visual inspection. Global noise was removed offline by subtracting external, non-biological noise recorded by eleven MEG reference channels. Offline treatment of the MEG signals was accomplished using the MATLAB-based open-source signal processing toolbox fieldtrip (Oostenveld et al., 2011), complemented by in-house MATLAB functions. TAU and BFP groups did not differ in terms of the number of artifact-free trials for oscillatory analysis (all comparisons n.s.) at t1 (BFP: 94.5 +/- 3.1, TAU 93.4 +/- 3.7), t2 (BFP: 95 +/- 3.2, TAU: 94.9 +/- 3.1) or t3 (BFP: 94 +/- 2.6, TAU: 95 +/- 3.3).

Oscillatory activity was analyzed in epochs extending from 200 ms prior to 1300 ms after S1. Spectral analysis was computed for each trial using a single Hanning taper with a window of fixed length of 1000 ms in sliding steps of 50 ms. Resulting power estimates were averaged over trials for each participant. First, evaluation of training effects considered relevant time-frequency windows based on previous results ( Carolus et al., 2014; Popov et al., 2012, 2015) that had shown modulations of induced 8-16 Hz (alpha) frequency range 300-800 ms after S1 onset in a posterior sensor cluster. Second, sensor clusters on the basis of which Time x Frequency x Group interaction were evaluated were determined by cluster-based, two-tailed independent-sample t- or f-tests with Monte Carlo randomization (Maris & Oostenveld, 2007) using a window of fixed 1000-ms length in sliding steps of 50 ms, resulting in 1-Hz frequency steps. The same procedure examined time-frequency windows of differences in alpha power modulation between HC and FE prior to intervention. Effects were verified for power change averaged for the respective sensor cluster by repeated-measures analyses of
variance with the between-subject factor Group (BFP vs. TAU) and the within-subject factor Time (t1 vs. t2, or t2 vs. t3, respectively).

Cognitive performance on the MCCB (footnote 8) was analyzed converting raw scores to T-scores based on a representative American community sample of healthy subjects (German norms have not been provided). Normal distribution was verified using the Kolmogorow-Smirnov test.

Relationships between change in alpha power modulation and change in cognitive performance were examined using the Pearson correlation.

4.4. Results

For the a priori selected time-frequency window 8-12 Hz, 300-800 ms after S1-onset, the pre-intervention alpha power decrease was larger in HC than in FE (Group (F(1,61) = 8.66, p < .01). In the same time-frequency window alpha power modulation at t2 did not differ between FE accomplishing BFP or TAU).

The time-frequency representation of power during the paired-click interval (Figure 10A) before and after intervention indicates differential effects of BFP and TAU in the alpha (8-12 Hz) range 0-600 ms after the first click in right-temporal-posterior regions: The Group x Time interaction (F(1,33) = 10.62, p < .01) resulted from greater alpha power change after BFP (F(1,19) = 18.19, p < .001) than after TAU (F(1,14) = 2.42, p > .2). This BFP-effect was particularly evident for 10-Hz alpha power decrease 400-700 ms after S1 onset (around S2; Figure 10C, Group x Time, F(1, 33) = 8.88, p < .01; Time, BFP, F(1,20) = 4.57, p < .05, TAU, F(1,14) = 4.18, p < .1, footnote 9). 14 BFP-completers and 2 of the 15 FE undergoing TAU (Chi²(1) = 10.99, p < .01) showed a change towards greater alpha power decrease. However, 6 TAU participants presented an alpha power decrease comparable to the modulation in HC at t1, which resulted in a significant main effect Group at t1 (F(1,33) = 6.34, p < .01). 17 FE conducting BFP were available for re-assessment three months after training (t3), while only seven TAU participants could be recruited (this prevented a Time x Group ANOVA including the three assessments and limits the validity of a Time x Group ANOVA comparing t2 – t3 or t1 – t3). Paired comparisons confirmed that the larger 10-Hz alpha power decrease at 400-700 ms after S1 onset remained stable across the three months in BFP (t2-t3, n.s.). In contrast, the BFP effect on S1-evoked 8-12 Hz alpha modulation (80-230 ms) was not stable over the follow-up period (t2 - t3, t(16) = -3.29, p < .01).
Figure 10
A: Time-frequency representation of power in response to S1 (abscissa: 0 s) and S2 (abscissa: 0.5 ms). Frequency changes between 0 and 20 Hz (ordinate) are depicted as the difference between stimulus-induced change from baseline after compared to pre-intervention (in decibel, see color bar). Intervention-induced TFR differences are shown separately for patients assigned to BFP (left) and TAU (right). Cold colors indicate a greater change (decrease) in power from baseline following intervention, warm colors indicate no decrease or an increase in power relative to baseline post- compared to pre-intervention. Dashed black rectangles mark the time-frequency window of significant change by intervention (top) between groups (bottom).
B: Topographical representation of the sensor cluster of significant Group (BFP vs. TAU) x Time (post- vs. pre-intervention) interaction. Color-coding depicts the statistical effect with warm colors representing larger group differences (t-values); black dots signal sensors composing the cluster of significant interaction.
C: Group differences (BFP vs. TAU) in alpha power change from baseline post- relative to pre-intervention 400-700 ms after S1-onset in the 10-Hz band, illustrated as a time-frequency representation (TFR) of statistical power (left) and a topographical projection of the significant Group x Time interaction (right). TFR represent changes in power (frequency range 0-20 Hz, ordinate) after S1-onset (abscissa: 0 s) relative to a 200-ms pre-S1 baseline, with warm colors indicating greater changes after BFP relative to pre-intervention than after TAU. The dashed black rectangle indicates the time x frequency window of significant group (BFP vs. TAU) x time (post vs. pre) differences, for which the respective sensor cluster of significant Group x Time interaction is depicted in the topographical representation (left). The color bar corresponds with statistical differences with warm colors indicating greater group x time differences (t-test). Black dots indicate sensors in the cluster of significant Group x Time interaction.
In the small TAU group, evoked and induced alpha power modulation did not significantly differ between pre-, post-, and follow-up assessment. Cognitive test performance (MCCB) improved in FE without differences between BFP or TAU (Time, t1 - t2, F(1,33) = 21.4, p<.01, t1 - t3, F(1,21) = 34, p<.01, interactions n. s.; see Supplementary Table 8 and Carolus et al., 2015).

4.5. Discussion
Prominent cognitive deficits and dysfunctional brain activity early in psychotic development advocate for intervention to dampen or prevent cognitive decline (Gopal, 2005; Østergaard et al., 2014). Beneficial – though still insufficiently strong – effects of CRT further call for the evaluation of intervention strategies that address neural mechanisms of cognitive (dys)functions. In the present FE sample, a respective targeted training affected abnormal modulation of oscillatory activity more than TAU. As alpha power decrease is thought to index activation of a cortical area (Jensen & Mazaheri, 2010) and as alpha power modulation has been shown to be disturbed in schizophrenia patients (Abeles & Gomez-Ramirez, 2014; Carolus et al., 2014; Popov et al., 2011), results suggest that this potentially disrupted engagement in neuronal processing can be modified through training. If dysfunctional neuroplasticity signals pathophysiology in schizophrenia (Buonanno, 2010; Cavuş et al., 2012; Merzenich et al., 2014; Nieto et al., 2013; Rosen et al., 2015), the possibility to modify this characteristic suggests sufficient reorganization potential in patients. Moreover, the similarity of effects in present FE and chronic patients (Popov et al., 2015) indicates that neuronal learning and cortical reorganization is neither reduced by long-term neuroleptic treatment or chronicity nor particularly unstable early in the course of illness.

Other than in chronic patients who exhibited TT effects in the 8-16 Hz range (Popov et al., 2012, 2015), effects on induced alpha power decrease around the second click were limited to 10-Hz alpha. This may reflect the modulation of 10 Hz in most patients, while modification within the wider alpha band varies with individual variability within the group: a number of patients exhibited induced alpha power modulation in the broader frequency range (8-16 Hz) and latency window (300-800 ms) comparable to healthy controls prior to intervention, which impaired additional training effects. High interindividual variability is frequently reported in studies involving chronic and FE schizophrenia: ‘Patients diagnosed with schizophrenia may present with very different symptoms and accordingly would show different
neurophysiological aberrations from healthy controls. Therefore, EEG, fMRI, or PET results may strongly differ between small groups of schizophrenics’ (Lehmann et al., 2014, p. 2; see also Joyce et al., 2005). The variability of training-induced cognitive gains within schizophrenia samples has been partially associated with a common variation in the COMT gene (Fisher, 2009; Panizzutti, 2013). Thus, the variable intensity of TT effects may to some extent result from the individual ‘underlying biosignature’ (Panizzutti et al., 2013, p 264). In addition, the specific training-induced modification of 10-Hz power might indicate abnormality early in the generation and modulation of alpha oscillations (e.g., Wada et al., 1994).

Other than chronic patients (Popov et al., 2012, 2015), FE showed modification of the alpha power decrease time-locked to S1 (80-230 ms) after BFP, but not after TAU. S1-evoked alpha power modulation has been associated with attention deployment and stimulus encoding, and adequate attention deployment and stimulus encoding can be considered prerequisites of maintenance facilitating subsequent stimulus differentiation.

Training-induced augmented alpha power modulation around the second click prevailed over a three-month follow-up period. This interval is too short to imply the stability of reorganization effects, and the number of dropouts (especially in the TAU group) did not allow for adequate testing. The stability of training effects has been reported for cognitive measures (Fisher et al., 2010) and serum BDNF (Vinogradov, Fisher, Warm, et al., 2009). The evaluation of the long-term stability of training effects on oscillatory activity together with outcome measures such as global functioning, relapse or transition to chronic psychosis is needed in order to make further conclusions.

Cognitive function improved across time, independent of intervention (TT or TAU) and of training effects on oscillatory activity. This is in agreement with CRT effects (Bechdolf et al., 2012; Fisher et al., 2014; Mendella et al., 2015; Østergaard et al., 2014) and argues for cognitive training in early stages of psychoses. However, the lack of specific TT effects on cognitive performance as well as of correlation between test performance and alpha power modulation does not support the proposal (Merzenich et al., 2014; Merzenich, 2013) that effects on low-level processing (e.g., alpha-modulation-mediated stimulus differentiation) affect higher-level processing manifest in attention, verbal learning or working memory test performance. Various influences may have fostered the lack of correlation: the cognitive tests might not have been sensitive to the targeted processes, or effects may not have been strong enough to observably add to the general improvement.
A major limitation of this study is the number of dropouts from the TAU group during intervention and follow-up. It can only be speculated that daily TT within a neuroplasticity-oriented context created more commitment than the normal inpatient environment. Less incentive motivation has been observed in FE compared to healthy participants (Murray et al., 2008). Moreover, Nahum et al. (2014). Fisher et al. (2014) emphasized motivation and (monetary) incentives as factors that modify training commitment and effects. FE did not receive a financial bonus for participating in BFP; thus, incentive-based motivation was similarly low in both groups. For TAU, the lack of daily training appointments may have facilitated a loss of motivation to return for additional test and MEG assessments. The high dropout rate adds to the limitation of a heterogeneous sample. Small sample sizes have already been seen as a shortcoming of controlled clinical trials in clinical settings in general (Richard S E Keefe et al., 2013). It may be even more difficult to overcome in FE, who are released faster than chronic patients and may be less committed to longitudinal studies. An additional limitation may result from the duration of training: stronger effects might be expected in longer training periods. Combining a similar training protocol to the one described here with other CRT components, Vinogradov and colleagues realized between 40 and 100 sessions in an outpatient context (e.g., Fisher et al., 2009, 2015; Hooker et al., 2014; Panizzutti et al., 2013). Finally, the impact of medication on test performance and learning cannot be ruled out, although evidence for this is diverse: Vinogradov et al. (2009) report a significant association between serum anticholinergic activity, MCCB test performance, and TT; Moritz et al. (2013) emphasize the dampening effect of antipsychotic medication on test performance, while a meta-analysis (Fatouros-Bergman et al., 2014) could not substantiate such medication effects.

In conclusion, the present results indicate an impact of TT early in psychotic development and the possibility to modify disrupted alpha regulation as a contribution to early manifest cognitive dysfunction. This implies a potential for cortical reorganization and argues for the use of TT for early intervention. Considering the devastating personal and social consequences of cognitive functional decline in psychosis as well as the high economic costs of chronic schizophrenia (Reeder et al., 2014), TT offers a promising component of CRT.
5. Targeted Training Modifies Oscillatory Brain Activity in Schizophrenia Patients

5.1. Abstract

Effects of both domain-specific and broader cognitive remediation protocols have been reported for neural activity and overt performance in schizophrenia (SZ). Progress is limited by insufficient knowledge of relevant neural mechanisms. Addressing neuronal signal resolution in the auditory system as a mechanism contributing to cognitive function and dysfunction in schizophrenia, the present study compared effects of two neuroplasticity-based training protocols targeting auditory–verbal or facial affect discrimination accuracy and a standard rehabilitation protocol on magnetoencephalographic (MEG) oscillatory brain activity in an auditory paired-click task. SZ were randomly assigned to either 20 daily 1-hour sessions over 4 weeks of auditory–verbal training \( (N = 19) \), similarly intense facial affect discrimination training \( (N = 19) \), or 4 weeks of treatment as usual \( (TAU, N = 19) \). Pre-training, the 57 SZ showed smaller click-induced posterior alpha power modulation than did 28 healthy comparison participants, replicating Popov et al. (2011b). Abnormally small alpha decrease 300–800 ms around S2 improved more after targeted auditory–verbal training than after facial affect training or TAU. The improvement in oscillatory brain dynamics with training correlated with improvement on a measure of verbal learning. Results replicate previously reported effects of neuroplasticity-based psychological training on oscillatory correlates of auditory stimulus differentiation, encoding, and updating and indicate specificity of cortical training effects.
5.2. Introduction

The striking prominence of cognitive impairment and its impact on functional outcome in schizophrenia (Nuechterlein et al., 2011; Fioravanti et al., 2012; Heinrichs et al., 2013) has fueled the search for effective treatment and prevention and for clarification of neural contribution to cognitive deficits (see Thorsen et al., 2014, for review). Despite promising effects of cognitive remediation treatment (CRT), overall effects have been found to be only mild to moderate (Grynszpan et al., 2011; Wykes et al., 2011; Thorsen et al., 2014), emphasizing the need to consider neural mechanisms of cognitive (dys)function (Silverstein and Wilkniss, 2004; Merzenich et al., 2014) when designing function-specific training. For example, hemodynamic neuroimaging studies using domain-specific tasks (e.g., n-back for working memory) have shown CRT effects on frontocortical activity, supporting the hypothesis of impaired fronto-cortical capacity, potentially related to progressive structural abnormalities (Thorsen et al., 2014).

One model influencing the development of function-specific training advocates that cognitive dysfunction in schizophrenia results from fundamental weaknesses in perceptual and cognitive processing, which in turn are associated with poor neuronal signal resolution, slowed processing speed, impaired generation of sustained activity, or ‘noisy brain system processing’ (Winterer et al., 2000; Harrison and Weinberger, 2005; see also Minzenberg et al., 2009; Merzenich et al., 2014). If neuronal signal resolution fosters higher-order cognitive processes (Merzenich et al., 2014), CRT methods should target fundamental aspects of input representation and discrimination. Evidence of training-driven neuroplasticity and neuroplasticity-based structural and functional changes suggests that efficient training protocols should (a) be targeted, i.e., address specific deficits potentially related to fundamental illness features such as signal discrimination, and (b) consider necessary and optimal conditions for neuroplasticity (Elbert and Rockstroh, 2004; Merzenich, 2013; Merzenich et al., 2014). Protocols implementing this concept to foster neuroplasticity by training auditory–verbal discrimination accuracy and verbal working memory (e.g., Brain Fitness Program, BFP, Posit Science, SF, USA; referred to as Cognitive Exercises, CE, in Popov et al. 2011a and Popov et al. 2011b, and Popova et al., 2014) improved cognitive performance and prompted changes in electromagnetic measures of auditory signal processing (P50/M50, N100/M100, and P300 components of the event-related potential or field) that are often reported abnormal in schizophrenia patients (SZ; reviews by Dale et al., 2010; Fisher et al. 2013 and Fisher et al.
2015; Merzenich et al., 2014; see also Popov et al., 2011a; Subramanian et al., 2012). Thorsen et al. (2014) argued that insufficient understanding of CRT mechanisms contributing to neural and cognitive changes limits treatment development.

The present study examined neural oscillatory activity as a mechanism of neuronal activity involved in stimulus encoding and differentiation, which play a critical role in perceptual and cognitive dysfunction. Adding to evidence of dysfunctional regulation of oscillatory dynamics in SZ (e.g., Popov et al. 2011b, Popov et al. 2012 and Popov et al. 2014; Popova et al., 2014; Uhlhaas et al., 2008; Uhlhaas and Singer, 2010), trial-by-trial evoked and induced oscillatory activity provides further information about the dynamics of stimulus processing and discrimination (Buzsaki, 2010; Jensen and Mazaheri, 2010; Hanslmayr et al., 2012). In the present approach time-locked activity, often termed evoked, reflects brain activity consistently associated in latency and phase with stimulus onset, typically apparent after averaging across trials. Non-time-locked activity, often termed induced, is measured in single trials and reflects brain activity changes prompted by a stimulus but variable in latency, thus lost in averages. Distinguishing time-locked and non-time-locked oscillatory activity may reveal mechanisms involved in normal perceptual and cognitive performance and disrupted in SZ. For example, in a previous study using a paired-click task, evoked and induced modulation of oscillatory activity in the alpha frequency (8–16 Hz) range (footnote 10) distinguished SZ and healthy controls, in that SZ showed less evoked 8–12 Hz power increase (relative to pre-stimulus baseline) to the first click and less induced 10–15 Hz decrease midway between clicks and before S2-onset (Popov et al., 2011b).

With an emphasis on induced alpha power modulation, oscillatory activity was measured in a paired-click task as a means to study mechanisms of auditory signal differentiation. Although the reduced evoked response to the second of two brief, identical clicks in rapid succession is commonly described as gating, interpreted as inhibition of redundant information (e.g., Bramon et al., 2004) or suppressed response during the refractory period following S1 (Mathiak et al., 2011), the task prompts S1 encoding and differentiation of S2 as identical stimuli, thus redundant. Therefore, and as the ratio of click-evoked event-related brain potentials or fields P50/M50 ratio reliably distinguishes SZ and HC (e.g., Adler et al., 1982; Bramon et al., 2004; Hanlon et al., 2005; Smith et al., 2010; Yee et al., 2010; Popov et al., 2011a; Carolus et al., 2014), effects of training were evaluated in the paired-click design in the previous (Popov et al., 2012) and the present study.
In Popov et al. (2012), targeted training (BFP, see above) normalized induced 8–10 Hz decrease in contrast to broad-spectrum cognitive remediation. Whereas, pre-training, small induced alpha power decrease varied with abnormally large M50 ratio, post-training, larger alpha power decrease in SZ varied with smaller M50 ratio, in line with an assumption of improved paired-click processing and differentiation. In the conceptual framework of alpha power decrease as a sign of increased readiness for information sampling and facilitated neuronal network processing (Klimesch, 1999; Jensen and Mazaheri, 2010; Hanslmayr et al., 2012) training-augmented alpha power decrease was interpreted as a sign of facilitated S2 differentiation vis-à-vis S1-encoding. Intense, targeted auditory training normalized both, S1-evoked and induced alpha-power responses in SZ (Popov et al., 2012). This result supported the hypotheses that oscillatory dynamics mediate stimulus differentiation, encoding, and updating and that this neural correlate of cognitive dysfunction (Merzenich et al., 2014; Thorsen et al., 2014) can be modified by targeted psychological training.

The present study replicated the protocol of Popov et al. (2012) in a new sample of chronic SZ and evaluated its specificity by comparing SZ undergoing the BFP protocol and SZ undergoing a newly developed intervention that targeted facial affect discrimination in a similarly intense, neuroplasticity-based learning context (footnote 11) Facial affect discrimination was chosen as a comparison target of training, since social–cognitive impairment is among the domains which most reliably distinguish between SZ and HC (Heinrichs, 2004; Mesholam-Gateley et al., 2009) and since impaired facial affect recognition, discrimination, and expression have been established as prominent elements of impaired social cognition in SZ, which are targets of cognitive remediation and more focused training protocols (Sachs et al., 2012; Wölwer et al., 2012). Therefore, a training protocol matching BFP except for a focus on facial affect discrimination instead of auditory–verbal discrimination accuracy was developed in order to compare training-specific effects on domain-specific brain correlates. Regarding facial affect recognition, Popov et al. (2013) observed a pattern of alpha power decrease over posterior (secondary-visual) regions and an increase in sensorimotor regions during the time window of correct identification of affect in pictures reflecting different degrees of happy or fearful expression. This pattern was smaller in SZ (Popov et al., 2014). Targeted facial affect training increased induced sensorimotor alpha power increase relative to auditory–verbal training and TAU, and alpha power increase after FAT correlated with improve-
ment of performance on the affect discrimination task over the 20 training sessions (Popova et al., 2014).

The primary hypotheses were, first, that previously reported effects of auditory–verbal discrimination training on oscillatory measures (Popov et al., 2012) would be replicated in an independent sample and, second, that effects on oscillatory dynamics in the auditory paired-click task would be specific to the targeted function — auditory information processing. Thus, oscillatory activity in the auditory paired-click task should change after auditory–verbal training but not after visual facial-affect training. Third, given the premise that modification of cortical signal discrimination is fundamental to higher cognitive function (Merzenich, 2013), training-specific improvement in auditory oscillatory dynamics should vary with improvement in verbal learning and memory performance in neuropsychological testing (compared to performance on visual learning and social cognition domains, which were expected to improve more after targeted facial affect training, the active control procedure in the present study, than after auditory–verbal training).

5.3. Methods and Materials

Participants: Inpatients were recruited from the university inpatient unit of the regional Center for Psychiatry and diagnosed by experienced senior psychiatrists or psychologists using the ICD-10 criteria. The inclusion criteria were normal intellectual function and no history of neurological condition or disorder, including epilepsy or head trauma with loss of consciousness. Prior to the first assessment, patients were randomly assigned to one of three treatment groups: BFP or facial affect recognition training (FAT; see Popova et al., 2014) protocols or the standard treatment-as-usual (TAU) regimen in the unit (see Fig. 11 for the recruitment process). Across the recruitment period, random assignment was continued until 20 patients per training protocol had accomplished pre-training assessment, training protocol, and post-training assessment. Due to dropouts, incomplete data sets at the different stages of the study phases, and insufficient MEG data quality, complete data for 57 SZ were available for final analyses. Of these, 44 SZ were diagnosed with paranoid–hallucinatory schizophrenia (ICD-code F20.0), 6 with schizoaffective disorder (ICD-code F25.1), and 7 with other F20.x diagnoses. Table 9 summarizes the sample characteristics. Training groups did not differ in age, gender distribution, IQ (assessed by a standard German test for premorbid intelligence, MWT-B; Lehrl, 2005), years of education, clinical status (Positive and Negative Syndrome Scale — PANSS; Kay et al., 1987), or chlorpromazine equivalent.
Neuromagnetic oscillatory activity and cognitive function before training were assessed by comparison of the SZ with a sample of 28 healthy comparison participants (HC). HC were screened with the Mini International Neuropsychiatric Interview (Ackenheil et al., 1999) to exclude psychiatric or neurological disorder. Patients were older than HC (see Table 9), while groups did not differ in gender distribution or years of education.

Figure 11
Schizophrenia patients (SZ) recruitment across the study protocol. Numbers in each box represent the number of SZ per study phase. Eligible: SZ meeting the inclusion criteria. Pre-assessment: SZ consecutively assigned randomly to one of the training protocols before the pre-training assessment of symptoms (PANSS), cognitive performance (MCCB), and MEG. Training protocols: BFP: Brain Fitness Program, FAT: facial affect training and TAU: treatment as usual. Recruitment and assignment were continued until at least 20 SZ per training group were enrolled in the training. 4-week training: number of SZ per training group starting the 4-week training. Post-assessment: number of SZ per training group completing the 4-week training and available for post-training assessment of symptoms, MCCB, and MEG. Considering the complete data sets and MEG data quality, pre–post data analyses are based on \( n = 19 \) SZ per group.

**Design and Procedure:** The study was approved by the ethics committee of the University of Konstanz and registered as a Clinical Trial (ClinicalTrials.gov Registration NCT01781000). The participants provided written informed consent prior to the study and received 30 € upon completion of each session. For SZ the MEG assessment was done pre- and post-training, each session consisting of the assessment of neuromagnetic activity during the paired-click task and cognitive performance on the MATRICS Consortium Cognitive Battery (MCCB) (Nuechterlein et al., 2008).
Table 9 Demographic and clinical information.

<table>
<thead>
<tr>
<th></th>
<th>Schizophrenia Patients</th>
<th>Healthy controls</th>
<th>Statistical difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age M (SD)</td>
<td>37.05 (9.06)</td>
<td>29.3 (9.5)</td>
<td>$F_{(1,83)} = 13.26^{**}$</td>
</tr>
<tr>
<td>Gender m/f</td>
<td>19/38</td>
<td>14/14</td>
<td>$Chi^2 (1) = 2.17$, n.s.</td>
</tr>
<tr>
<td>Years of Education M (SD)</td>
<td>15.0 (2.54)</td>
<td>14.55 (3.44)</td>
<td>$F_{(1,58)} &lt;1$, n.s.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Training Groups</th>
<th>BFP</th>
<th>FAT</th>
<th>TAU</th>
<th>Statistical difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age M (SD)</td>
<td>36.95 (8.44)</td>
<td>39.21 (7.91)</td>
<td>35.00 (10.59)</td>
<td>$F_{(1,54)} = 1.03$, n.s.</td>
</tr>
<tr>
<td>Gender m/f</td>
<td>6/13</td>
<td>9/10</td>
<td>4/15</td>
<td>$Chi^2 (2) = 3.02$, n.s.</td>
</tr>
<tr>
<td>Years of Education M (SD)</td>
<td>14.56 (3.29)</td>
<td>14.68 (4.19)</td>
<td>14.42 (2.99)</td>
<td>$F &lt;1$</td>
</tr>
<tr>
<td>IQ M (SD)</td>
<td>101.47 (13.46)</td>
<td>109.79 (16.13)</td>
<td>108.21 (17.89)</td>
<td>$F = 1.46$ n.s.</td>
</tr>
<tr>
<td>GAF M (SD)</td>
<td>44.68 (13.6)</td>
<td>42.32 (12.32)</td>
<td>42.73 (14.32)</td>
<td>$F &lt;1$</td>
</tr>
<tr>
<td>PANSS-P M (SD)</td>
<td>15.42 (5.18)</td>
<td>16.42 (5.27)</td>
<td>14.26 (5.08)</td>
<td>$F &lt;1$</td>
</tr>
<tr>
<td>PANSS-N M (SD)</td>
<td>18.21 (6.55)</td>
<td>18.58 (6.60)</td>
<td>18.84 (6.29)</td>
<td>$F &lt;1$</td>
</tr>
<tr>
<td>PANSS-G M (SD)</td>
<td>35.63 (85.39)</td>
<td>36.68 (8.50)</td>
<td>34.11 (8.98)</td>
<td>$F &lt;1$</td>
</tr>
<tr>
<td>CPZ M (SD)</td>
<td>544 (490)</td>
<td>671 (343)</td>
<td>617 (403)</td>
<td>$F &lt;1$</td>
</tr>
</tbody>
</table>

Note: GAF: Global Assessment of Functioning (DSM-IV axis V), PANSS: Positive and Negative Syndrom Scale, Scales P (positive symptoms), N (negative symptoms), G (general symptoms), CPZ: Chlorpromazine equivalents.

The two targeted training protocols were identical with respect to computer-based exposure, intensity, shaping, and reinforcement algorithm fostering neuroplasticity (Elbert and Rockstroh, 2004; Merzenich et al., 2014): 20 daily 1-hour sessions were scheduled on consecutive workdays across four consecutive weeks. A computer algorithm provided individual adjustment of task difficulty as a function of performance, and motivating feedback was
provided per task and session. BFP focused on auditory–verbal discrimination and memory, and FAT focused on facial affect recognition. BFP consists of 6 computerized exercises: judging gradually more difficult distinctions between frequency-modulation sweeps of auditory stimuli, distinguishing phonemes with synthesized speech, identifying arrays of open and closed syllables in spatial and temporal context, discriminating tone frequencies, and remembering details of short narratives. FAT (footnote 12) consists of four tasks, two emphasizing facial affect discrimination and two emphasizing facial affect recollection: deciding whether two different posers are displaying the same or different emotion, or which emotion is displayed by a face blended from two emotions from a single poser, recalling a sequence of emotion faces from a single poser, and recalling the location of identical pairs of poser/emotion combinations among an array of hidden faces (for details see Popova et al., 2014).

**Data collection:** Prior to MEG measurement, individual hearing levels were determined for each ear separately via an adapted method of limits (Gescheider, 1997). The paired-click procedure comprised 100 trials, each trial a pair of 3 ms square-wave clicks (S1 and S2) presented with a 500 ms onset-to-onset interstimulus interval within trial, with intervals between S2 and the subsequent S1 varying between 7 and 9 s. Clicks were presented 60 dB above individual hearing level and delivered via 5 m nonferromagnetic tubes. No performance task was involved, except that participants were asked to keep their eyes focused on a small fixation point throughout the procedure.

MEG was recorded while subjects were in a supine position, using a 148-channel magnetometer (MAGNES 2500 WH, 4D Neuroimaging, San Diego, USA). Data were continuously recorded with a sampling rate of 678.17 Hz and a bandpass filter of 0.1–200 Hz. Trials containing movement artifact or SQUID jumps were rejected based on visual inspection. Global noise was removed offline by subtracting external, non-biological noise recorded by an additional 11 MEG reference channels. Offline treatment of the MEG signals was accomplished primarily with the MATLAB-based open-source signal processing toolbox FieldTrip (Oostenveld et al., 2011). Epochs of 1000 ms before and 2000 ms after the first click (S1) of each trial were extracted from continuous recordings. BFP (M ± SD 95 ± 5), FAT (M ± SD 95 ± 3), TAU (M ± SD 95 ± 6) and HC (M ± SD 92 ± 6) did not differ in number of artifact-free trials ($F(3,81) = 1.88$, $p = 0.14$).
Data analysis: Single-trial time–frequency representation of power (TFR) was estimated using a sliding 500 ms window multiplied by a Hanning taper. Single-trial power estimates were then averaged across trials and expressed as a decibel change from a 200 ms pre-stimulus baseline. In a first step, identification of time–frequency windows of differences between SZ ($n = 57$) during the first assessment (prior to training) and HC ($n = 28$) served to replicate deficient induced alpha power decrease around S2 as described for an earlier, independent SZ sample (Popov et al., 2011b). Relevant time–frequency windows were defined using a cluster-based, independent-sample $t$-test with Monte Carlo randomization (Maris and Oostenveld, 2007) for identification of sensor clusters of significant Time $\times$ Frequency $\times$ Group interaction. Hypothesis-relevant activity was expected in the 8–16 Hz alpha frequency range during 300–800 ms post-S1 onset, thus including S2, which was presented at 500 ms. A one-way, four-level ANOVA on alpha power change from pre-S1 baseline evaluated responses to the clicks for the three SZ groups prior to training and the HC group.

In the next step, a Group (BFP, FAT, TAU) $\times$ Time (pre-, post-training) ANOVA on alpha power change from pre-S1 baseline assessed training effects for the three SZ groups, again using Monte Carlo randomization to define time $\times$ frequency $\times$ sensor clusters with a significant Group $\times$ Time interaction. Where appropriate, significant ANOVA effects were followed up with $t$-tests to aid in interpretation.

Cognitive performance in the SZ samples was assessed with the MATRICS Consortium Cognitive Battery (MCCB; Nuechterlein et al., 2008; German Translation Regents of the University of California, 2006; see Harvey et al., 2010). The MCCB covers seven domains of cognitive function that have been shown to be impaired in schizophrenia: processing speed, attentional vigilance, working memory, verbal learning, visual learning, reasoning, and social cognition. Raw scores were converted to $T$-scores based on a representative U.S.A. community sample of healthy subjects (Nuechterlein et al., 2008; German norms have not been developed). Normal distributions were verified with the Kolmogorov–Smirnov test. A Group (BFP, FAT, TAU) $\times$ Domain $\times$ Time (pre-, post-training) ANOVA assessed treatment effects. (The present report concentrates on the relationship between changes in performance per domain before and after targeted training or TAU and changes in induced alpha oscillations in the paired-click task. Detailed analyses of the MCCB profile in the SZ sample, including pre-training, post-training, and a 3-month follow-up measurement, are reported in Carolus et al.,
relationships between test performance and facial affect training effects are reported in Popova et al., 2014). Relationships between changes in cognitive test performance and changes in MEG oscillatory measures were tested by correlations of the change scores. The primary interest was in scores on the verbal learning test, to evaluate the specificity of the three types of intervention according to the third hypothesis.

5.4. Results

Figure 12 shows that evoked alpha power increased after S1 and that induced alpha power declined substantially around the onset of S2 in the HC group. Prior to training, SZ showed less evoked alpha power increase and less induced decrease around S2. Group differences in the evoked alpha power increase 50–300 ms after S1 likely reflect the S1-evoked M100 or M200, which is known to be smaller in SZ than in HC.

![Figure 12](image)

Schizophrenia (SZ) groups prior to training compared to healthy comparison participants (HC). Four panels to the left: for the HC and for the three SZ later assigned to the Brain Fitness Program (BFP), facial affect training (FAT), or treatment as usual (TAU), time–frequency representations of 0–20 Hz power (dB change from pre-S1 baseline) in response to S1 (0 ms) and S2 (500 ms) are illustrated for the sensor cluster in the topographical representation in the fifth panel. Dashed rectangles indicate the time window (300–800 ms) of significant change in alpha (8–12 Hz) power from baseline, with cool colors (thin color bar) indicating power decrease. Fifth panel: topographical map of statistical tests of group differences. Thick color bar reflects F-values (4-group ANOVA), with warm colors indicating larger alpha power decrease in HC than in SZ. Black circles identify the MEG sensors in the analyzed cluster. The power spectrum in the right panel illustrates similar pre-stimulus alpha power in HC (blue) and SZ (red). Shading indicates 1.0 SEM and shows group overlaps.

Within the 8–16 Hz frequency (footnote 10) and 300–800 ms time range, the Monte Carlo randomization identified significant group differences for 8–12 Hz between 400–700 ms (around S2 onset). Submitting the scores used in the Monte Carlo randomization test to a conventional one-way ANOVA verified a Group effect, $F(3,81) = 7.50, p = .002$. Post-hoc comparisons correcting for multiple comparisons did not show significant pre-training differences between any pair of SZ groups ($p = .2$). Fig. 13 illustrates the impact of training on induced alpha-power response to the click pair. Within the 8–16 Hz frequency range and the
300–800 ms time range, the Monte Carlo randomization identified a significant Group × Time interaction for 12–16 Hz between 300–800 ms (around S2 onset). The Group × Time interaction, $F(2,54) = 4.53$, $p = .015$, and post-hoc $t$-tests confirmed that BFP (effect size $d = -.84$) fostered more decrease in alpha-power response (thus, partial normalization), with no significant change for FAT ($d = -.12$) or TAU ($d = .52$). There was no effect of training on S1-evoked alpha power.

![Figure 13](image)

Schizophrenia-group training effects (calculated as post- minus pre-training) on MEG quantified as time–frequency representations of 0–20 Hz power changes (dB change from pre-S1 baseline) in response to S1 (0 ms) and S2 (500 ms) illustrated for the significant sensor cluster in the topographical map in the right panel. Dashed rectangles indicate the time window (300–800 ms) of significant change in alpha (8–14 Hz) power from baseline, with cool colors (thin color bar) indicating alpha power decrease.

Given that induced (and evoked) alpha power modulations could be driven by differences in prestimulus baseline activity, the power spectra were analyzed for the 1500 ms prestimulus interval. As evident in Fig. 12, groups did not differ in power spectrum during the baseline. Cognitive test performance improved from pre-training to post-training assessment (Time, $F(1,54) = 24.94$, $p < .001$; Domain × Time, $F(6,324) = 4.40$, $p < .001$, Huynh–Feldt $\epsilon = .92$), but there was no significant behavioral effect related to training group. Improvement over time occurred specifically for processing speed, attention, and visual learning (each simple main effect of Time $p < .001$). The main effect of Domain ($F(6,324) = 12.19$, $p < .001$, Huynh–Feldt $\epsilon = .92$) was not of interest. The only effect involving Group was a marginal Group × Domain × Time effect, $F(12,324) = 1.70$, $p < .08$, $\epsilon = .88$, providing limited evidence of specificity judged not worth interpreting.
Correlations evaluated the impact of training on each MCCB domain, following the third hypothesis that modification of cortical signal differentiation is fundamental to higher cognitive function. In line with this premise, Fig. 14 illustrates a group-specific contribution to the relationship between the training effect on decrease in alpha power around S2 and the change on verbal learning performance. Greater induced alpha power decrease around S2 predicted greater improvement in verbal learning after training in the BFP group (Spearman's $r = -0.7$, $p < 0.01$) but not in the FAT group ($r = -0.1$, $p < 0.5$) or TAU group ($r = 0.03$, $p < 0.5$). The negative BFP correlation differed significantly from the positive TAU correlation. The intermediate FAT correlation did not differ reliably from either. Correlations of training effects with other MCCB tests were non-significant.

![Figure 14](image)

**Figure 14**
Scatterplot (right panel) of training effects (BFP = Brain Fitness Program, FAT = facial affect training, TAU = treatment as usual) on change in alpha power suppression (8–12 Hz) from pre-S1 baseline during 300–800 ms after S1 onset (left panel) for a left posterior sensor cluster (middle panel) vs. training effect on performance on the MCCB verbal learning test. Cool colors for the correlation values in the color bar indicate association of larger (more normal) post-S1 decrease post-training than pre-training with higher verbal learning score post-training than pre-training. BFP and TAU slopes differed (homogeneity of regression $F = 6.4$, $p < 0.02$). Other pairs of slopes did not differ.

5.5. Discussion

Impairment in neuronal signal resolution, processing speed, and neuroplasticity has been proposed as fundamental to SZ pathology, substantially contributing to characteristic features such as cognitive deficits and functional decline (e.g., Buzsaki and Watson, 2012; Merzenich et al., 2014; Uhlhaas et al., 2008). The present results of less induced alpha power decrease in the processing interval between pair-wise presented identical stimuli in SZ replicate Popov et al. (2011b). The present results showing that training can ameliorate this deficit replicate Popov et al. (2012). Comparison with an active control training provides evidence of the specificity of an intervention mainly affecting a neural mechanism involved in processing of auditory signal differentiation.
Induced alpha power decrease before or around stimulus presentation is believed to reflect the readiness of relevant neuronal assemblies for information intake (Jensen and Mazaheri, 2010) and to facilitate differentiation and matching of temporally adjacent stimuli. This suppression of activity in the alpha frequency range before and around stimulus processing is smaller in SZ than in HC (Popov et al. 2011b and Popov et al. 2012; Carolus et al., 2014). The present results show that this deficit can be at least somewhat normalized by targeted auditory-signal discrimination training, replicating results for a previous sample reported in Popov et al. (2012). Both studies showed larger induced power decrease within the alpha frequency range, though differing slightly in the frequency window of significant group and training effects. Given that individual alpha power characteristics and effects of intervention or experimental manipulation vary between individuals within the range of frequencies assigned to ‘alpha’ (see references in footnote 10), slight differences in statistically significant effects between studies do not undermine the similarity of effects.

The present results provide evidence of specificity of targeted training addressing a supposedly dysfunctional system. Fig. 13 illustrates more improvement in oscillatory dynamics during the auditory paired-click task after auditory-verbal training than after facial affect training or treatment as usual. Fig. 14 illustrates a group-specific contribution to the relationship between the training effect on decrease in alpha power around S2 and the change on verbal learning performance, even though performance on verbal learning tests (MCCB) did not improve specifically for the SZ sample overall.

Given the proposal (Merzenich, 2013; Merzenich et al., 2014) that problems in low-level processing underlie problems in higher-level processing, one would hope that a training protocol that targets low-level processing might have benefits extending beyond cognitive tests closest to the target function. Such a pattern was not observed in the present data set, in line with findings for a similar training protocol by Fisher et al. (2015). Merzenich (2013) and Merzenich et al. (2014) proposed neuronal signal resolution as constituting a fundamental neuronal dysfunction in schizophrenia, thereby influencing many basic processes involved in perception, information discrimination, learning, and memory. All these processing elements may be supposed to contribute to cognitive dysfunction at a higher level. Yet it may be too far-reaching to assume that this influence of basic effects on higher-order cognitive functions is reflected in a strong correlation between brain measures of fundamental neuronal signal resolution deficit and test performance. A lack of correlation between such distant
levels may result from various influences. For example, cognitive tests may not be sensitive to the specific neuronal process that was modified by training, and many intermediate steps between neural signal resolution and test performance are not measured (Miller and Rockstroh, 2013). Additional behavioral measures reflecting neuronal mechanisms of stimulus perception and differentiation could be added in future studies in order to verify the proposed link between dysfunction at a neuronal level and higher order cognitive function.

Cognitive performance on a test battery specifically designed to capture cognitive deficits in schizophrenia improved over the 4-week period, during which targeted training or the standard treatment regimen (TAU) took place. This was a period of symptom improvement. The present finding of a null effect of cognitive training suggests that the impact of targeted cognitive training was not strong enough to visibly add to the general impact of symptom remission on cognitive improvement. Possible shortcomings of the training protocol (brief duration) or the assessment of cognitive functions (appropriateness of MCCB to capture key training elements) could be explored before concluding whether the present targeted, neuroplasticity-based training protocols affect cognitive performance. For example, the present procedures included 20 1-hour training sessions and evaluated training effects after the end of 4 weeks of training, whereas studies employing a similar training protocol reported stronger effects after 40–50 or more training sessions and a 6-month follow-up. The present restriction to 20 sessions and immediate post-training assessment reflect the inpatient status of the present sample and the administrative priority placed on reducing inpatient treatment duration. The extent to which the present effect sizes were influenced by sample characteristics (more severely impaired inpatient), brevity of training, or brevity of follow-up cannot be evaluated in the present data set and warrants study.

The domain-specific pattern of results was not as strong or consistent as has been reported in some other studies (e.g., Fisher et al., 2015). Across training groups, overall improvement was observed for processing speed, attention, and visual learning domains but not for domains presumably closer to the auditory–verbal focus of BFP, verbal learning and perhaps working memory. Both BFP and FAT involved visual and auditory stimulation (BFP using auditory stimuli for discrimination training and visual stimuli for task instruction and reinforcement, FAT using visual stimuli for affect discrimination training and task instruction with auditory reinforcement), and both included an emphasis on working memory training. These shared features may have obscured specific effects, but it is unclear as to why these domains
did not benefit specifically from training. On the other hand, BFP alone fostered a relationship between alpha normalization and verbal learning improvement, providing some evidence of specificity. Moreover, improvement in test performance in the MCCB working memory and verbal learning domains was found in an overlapping sample at a follow-up 3 months after training (Carolus et al., 2015). This evidence, though suggestive, may not be sufficient to conclude that training effects on particularly impaired functions (like working memory or verbal learning) unfold slowly. Third, limited training effects may be a function of the tests used to probe their impact. In an independent sample Popov et al. (2012) used verbal learning and working memory tests from the German version of the California Verbal Learning Test (VLMT, Helmstädter and Lux, 2001) rather than from the MCCB. Without systematic, direct comparison of the respective tests, this possible factor cannot be evaluated. Further limitations of the present study should be considered. The impact of medication on test performance and training effects must always be considered. It has been suggested that antipsychotic medication can generally dampen effects on cognitive test performance (Kane, 2011; Moritz et al., 2013). However, a recent meta-analysis found no difference in cognitive test performance in medicated and drug-naive SZ (Fatouros-Bergman et al., 2014). It has also been suggested that antidopaminergic effects of neuroleptics impair learning and neuroplastic capacity (Pessiglione et al., 2006). However, given the general treatment intention to achieve low maintenance dosage, and given the fact that medication (CPZ) did not differ significantly between pre- and post-assessment (t(53) = 1.29, p = .2) and did not vary with changes in alpha power decrease or cognitive test performance, a substantial influence of medication on the present results seems unlikely.

Moreover, the patient sample accomplishing BFP was older on average than the healthy control sample. Given that the primary goal of the study was the evaluation of training effects within patients – and, for the entire project, between patient groups accomplishing two different types of targeted training – the HC group served merely to verify the typical pretreatment patient abnormalities reported in the literature. Thus, the HC group was smaller than the overall patient sample, matching the entire sample of n = 57 patients included in the project in average age and gender distribution. By chance, matching for the patient sample assigned to BFP did not occur for age, whereas a better match was achieved for the FAT group, which did not differ in age from HC (Popova et al., 2014). Though the lack of one-to-one matching of an HC group of the same size as the entire SZ sample is a limita-
tion of the present project, it should be noted that HC matching here was not intended to control for training effects but only to verify well established pre-training abnormalities, which was successful.

5.6. Conclusion

In summary, the present results replicate evidence for disruption of a neural oscillatory mechanism in schizophrenia and for the potential of targeted training to improve neural and cognitive function. The present results also indicate specificity of targeted training addressing a dysfunctional system.
6. General Discussion

Almost every article on schizophrenia contains phrases like ‘severe mental illness’, ‘cognitive deficits as a core feature’, ‘progressive disease’, ‘worsening with course’ and ‘degeneration’. These words allude to schizophrenia as an illness with a chronic course, and often foster the assumption that symptoms and abnormalities are a product of chronic illness. Are the core features such as cognitive decline and abnormal brain parameters (for example altered oscillatory dynamics) described in schizophrenia really a sign of chronicity or can they be seen as pathophysiological markers which manifest in the early stages of the psychotic disorder? If an early manifestation of these parameters is evident in FE patients, is there the potential for modification?

The present thesis addresses these questions by evaluating the cognitive profiles and oscillatory dynamics in FE schizophrenia patients. A neuroplasticity-oriented training which had been shown to be successful in modifying altered oscillations in chronic patients (Popov, et al., 2012, 2011a) was used to evaluate its effectiveness and feasibility in FE patients. The most prominent results of the present thesis are that cognitive deficits and abnormalities in alpha oscillations manifest early in the course of illness and that training can modify them.

In the following two sections, early manifestation, flexibility and clinical relevance for the assessed cognitive and brain parameters are discussed separately.

6.1. Perspective on cognitive functions in first-episode patients

Early manifestation:

The results from study one and two support the claim that cognitive dysfunctions can be seen as a core characteristic in schizophrenia: all schizophrenia patients in the present study – FE and chronic patients – exhibit striking abnormalities in all cognitive domains as assessed with the MCCB when compared to healthy controls (Hedges’ g 0.74 – 1.72).

Cognitive abnormalities are not only a key characteristic in chronic patients but they are already evident in FE patients (with a similar pattern and magnitude as in chronic patients), thus contributing to psychopathology. The neurodevelopmental hypothesis for schizophrenia (Weinberger, 1987) claims that the primary pathology in schizophrenia is a failure during brain maturation, from which both, behavioral deficits and neurobiological abnormalities evolve (see also Lewis & Levitt, 2002; Pino et al., 2014; Rund, 2009). As studies point towards
the occurrence of cognitive abnormalities long before the outbreak of the illness (e.g. Reichenberg et al., 2010; van Oel et al., 2002) and in healthy relatives (Snitz, Macdonald, & Carter, 2006), genetic contributions can be assumed. The relation of genes to the behavioral outcome (e.g. cognitive deficits) is a topic of research but there is evidence that genes predispose to central pathophysiological processes in schizophrenia in a convergent fashion. Genes involved in cell migration, synaptogenesis, cell proliferation, axonal outgrowth and myelination have been found to be affected in subjects with schizophrenia (for an overview see Fatemi & Folsom, 2009). Harrison & Weinberger (2005) suggest genetic influence on synaptic plasticity, which in turn affects NMDA-receptor mediated glutaminergic transmission that disrupts neuronal microcircuits involved in higher order cortical functions like executive control processing. They therefore provide a potential linkage between the genetic mutations and the observable symptoms (e.g. the cognitive deficits assessed in the present study). The role of the glutamate/NMDA receptor-systems and the related dopaminergic systems on altered neuroplasticity on synaptic- and network-level has been repeatedly emphasized (e.g. Arnold et al., 2005; Carter, 2006; du Bois & Huang, 2007; Steullet et al., 2006). Uhlhaas (2011) emphasizes the evidence of abnormal brain development during adolescence that influences the outbreak of schizophrenia and therefore proposes a ‘late’ neurodevelopmental model. This view is supported by research that demonstrates loss in grey matter volume during adolescence as a normal developmental process of a healthy brain (Gogtay et al., 2004), a process that has been shown to be exaggerated and pattern-specific in schizophrenia (Hulshoff & Kahn, 2008; Rapoport et al., 1999, see also chapter 1.4 in this thesis).

There are many genetic and environmental factors contributing to and developmental processes disrupted in schizophrenia. The cognitive deficits observed in the present study in FE patients can be seen as a reflection of these various pathological developmental abnormalities or as ‘the outcome of aberrant neurodevelopment continuing throughout the first two or three decades of life’ (Bora, 2015). Regardless of the exact point in time at which the cognitive deficits begin and the specific developmental processes that are involved, the present study demonstrates striking abnormalities early in the course of the illness and therefore advocates a feasible treatment for young patients that tries to target and improve these deficits as efficiently and early as possible. The effects of intervention on the cognitive deficits are analyzed in the second study.
Flexibility:

Study two demonstrates the cognitive deficits as not static or worsening progressively, but showing some flexibility: although they were not ‘cured’ and the level of the healthy comparison group was not achieved, cognitive deficits improved over time. This improvement was independent of training. The results again motivate hypotheses on the nature of the pathology of cognitive deficits, as the neuronal underpinnings could not be fixed by medication or psychological intervention, even with neuroplasticity activated as in the present study. Compensatory processes may possibly be strengthened, thus alleviating or preventing further decline.

The improvement in all groups was beyond the normal practice effects (for the MCCB Cohen’s d 0.03- 0.2; Keefe et al., 2011), the reasons for this can only be speculated on. Perhaps the standard treatment that also contained components aimed at improving cognitive deficits led to an amelioration so that the BFP could not contribute any additional effects. The improvements remained stable over the follow-up period of three months; although this result has to be interpreted with caution as many patients did not show up for reassessment (potential reasons for the high number of drop-outs are discussed in section 6.3). Additionally, the follow-up period was too brief to provide any information about long-term effects. Cognitive functions could worsen again, they could remain stable or effects of the specific trainings could emerge after some time.

Clinical implications:

Cognitive deficits and similarly negative symptoms have the reputation of being very hard to treat and of often being resistant to medication. Evidence that cognitive deficits are already present at the beginning of the illness advocates early intervention. Knowledge of these deficits showing flexibility is of high clinical relevance and raises therapists’ and patients’ hopes that these deficits do not have to be accepted but that something can be done. The present study was able to demonstrate that cognitive deficits are not static once they are present but can be treated so that improvements can be achieved.

All patients received routine care including neuroleptic medication, group therapy sessions, physical exercise, and cognitive behavioral psychotherapy sessions adapted to individual needs. The reasons for no additional improvements ‘on top’ in the BFT-receiving group can only be speculated: Perhaps, young, FE patients have higher or other demands on computer-based trainings, which were not met by the present training program. Their growing up to-
day, surrounded by new technologies like for example the internet, mobile phones and computer games might mean that modern trainings have to meet the criteria and provide the features that young people are used to in order to receive higher commitment. A possibility could be providing the training on laptops or tablets and therefore offering the flexibility where and when to complete a training session (an approach that was successfully used by Fisher and colleagues in 2014) and adapting the graphical interface, the ‘rewards’ and the structure of trainings in a computer game-like fashion. Studies that make use of new media in different aspects of therapy for schizophrenia patients are slowly emerging and yield promising results (e.g.: Ben-Zeev et al., 2014; Veling et al, 2014). Further potential reasons why the specified training had no additional effects on the cognitive functions might be the (possibly too low) number of training sessions or the MCCB as an insensitive outcome measurement and are discussed in section 6.3 of this thesis in more detail.

6.2. Perspective on altered oscillatory dynamics in first-episode patients

*Early manifestation:*

Equivalent to the cognitive measures, study one provides evidence that typical gating abnormalities are also present in FE patients, establishing reason to explore the associated oscillatory phenomena. Results reveal that abnormal alpha power decrease in the double-click paradigm is present in the early course of the illness, thus reflecting or contributing to psychopathology. As for both, gating ratio and oscillations measures, FE and chronic patients did not differ from each other in a relevant manner.

Similar to structural abnormalities found in schizophrenia patients (section 1.3), some oscillatory alterations seem to already be present at the onset of the illness (and probably even earlier, e.g. Alexander et al., 2009; Missonnier et al., 2012) whereas others evolve during the illness. For example, a recent study found altered low-frequency resting EEG in chronic but not in high-risk and FE patients (Ranlund et al., 2014). The study’s authors conclude that the abnormalities are probably related to illness progression and/or to long-term effects of treatment. For the present study, it seems unlikely that the observed oscillatory alterations are a product of illness progression and they can be ruled out as a consequence of long-term treatment as the patients who participated had not received long-term treatment yet. However, the results do not allow us to draw any conclusions as to when and why oscillatory abnormalities start to occur.
Alpha power desynchronisation, observed during the double-click paradigm and one of the most prominent markers in chronic patients in previous studies (Popov et al., 2012, 2011), was investigated in FE patients in the present study. Other oscillatory abnormalities may be present in the FE sample; nevertheless, the focus of this thesis is the role of alpha power in the early course of illness and its potential contributions to pathophysiology, topics that are discussed in the following section.

It has been suggested that alpha increase reflects an inhibition of those regions not required for the task whereas a decrease might be responsible for active information processing in the sense of excitatory brain processes (Klimesch 2007). The inhibitory nature of alpha was also considered in the ‘gating by inhibition’ hypothesis (Jensen & Mazaheri, 2010) which predicts a correlation between optimal task performance and alpha increase in disengaged and a decrease in engaged regions. In the present study, abnormalities in alpha desynchronisation were observed during the double-click design. Induced alpha power decrease before and around stimulus presentation is believed to reflect the readiness of relevant neuronal assemblies for information intake (Jensen & Mazaheri, 2010) and to facilitate differentiation and matching of temporally adjacent stimuli. Alpha modulation (in both directions) might indicate a suppression and release of top-down inhibitory control. Therefore, abnormalities in this modulation might signal an underlying neural mechanism of the pathophysiology in schizophrenia. Impaired alpha desynchronisation, which may indicate dysfunctions in alpha-generating mechanisms or in the cortical connections, is evident in ultra-high risk patients, becoming increasingly impaired with the progression of psychosis (Koh et al., 2011).

Similar to cognitive deficits, it can be speculated that abnormal oscillatory activity is a reflection of neurodevelopmental alterations in schizophrenia. The resulting changes in anatomy and neurotransmitter systems might have consequences on generators of neural oscillations and their synchronization. As the synchronization of oscillations is seen as a prerequisite for the development of cortical circuits during early development periods, aberrations during that period might play a central role in the pathophysiology of schizophrenia (Uhlhaas & Singer, 2010). Alterations in thalamocortical and cortico-cortical loops have been demonstrated in schizophrenia patients, possibly due to gene-driven reductions in spine density (Glantz & Lewis, 2000) and somal volume (Pierri et al., 2001). It has been proposed that the same circuits or loops play a major role in the generation of alpha rhythm in human brains (Lopes da Silva & Storm Van Leeuwen, 1977; Lopes da Silva et al., 1980; Schreckenberger et
It may be hypothesized that the disruption of alpha generating loops and circuits early in the brain maturation process might influence the alpha generation, therefore leading to the aberrant pattern observed in FE patients in the present study.

**Flexibility:**
The modifications of alpha dynamics by the auditory BFP as demonstrated in studies three and four can be seen as a reflection of neuroplastic potential, although a direct measurement of neuroplasticity was not conducted.

Applying the model of Merzenich (2014), cognitive dysfunction in schizophrenia results from fundamental weaknesses in perceptual and cognitive processing, which in turn are associated with poor neuronal signal resolution, slowed processing speed, impaired generation of sustained activity, or ‘noisy brain system processing’ (Winterer et al., 2000; Harrison and Weinberger, 2005; see also Minzenberg et al., 2009; Merzenich et al., 2014). The BFP is designed to train patients to ‘refine representational fidelity and operate at speed, in ways designed to reduce internal brain noise and restore more normal physico-chemical processing’ (Merzenich et al., 2014, p. 7).

In studies three and four, modifications on a supposedly dysfunctional system could be demonstrated for FE and replicated for chronic patients. As alpha power modulation has been shown to be disturbed in schizophrenia patients (Abeles & Gomez-Ramirez, 2014; Popov et al., 2011), results suggest that this potentially disrupted engagement in neuronal processing can be modified through training, therefore demonstrating reorganizational potential in patients independent of illness status (FE and chronic). There was no effect of training on the ‘higher’ cognitive functions (as discussed in section 6.1 and 6.3), possibly due to an insensitivity of the MCCB to the specific neuronal process that was modified by training.

**Clinical implications:**
Study one provides evidence of disturbed neuronal dynamics in schizophrenia. Although not obvious at the first sight, knowledge about these abnormalities is of high clinical relevance. The observed cognitive deficits – a core feature of schizophrenia illness that has far-reaching consequences for patients – is suggested to be a result of disturbed communication within brain networks, as measured by aberrant oscillations. Uhlhaas (2015) suggests schizophrenia illness resulting from a two-stage model: The main process and therefore the primary pa-
thology is the disturbance of temporal coordination in large-scale networks and the resulting cognitive deficits. A secondary (maybe compensatory) process causes the positive symptoms. This interpretation emphasizes the importance of cognitive deficits and advocates the future development of biomarkers to gain better diagnostic information, to identify clinical subgroups and – on the very long run – pave the way for personalized therapies.

Studies three and four indicate that a supposedly dysfunctional neuronal system is still flexible in schizophrenia patients. Demonstrating a modification of altered oscillatory dynamics in a correcting direction emphasizes the importance of specific training programs in clinical settings.

Of course, in order to be of high clinical and practical relevance, trainings should not only demonstrate an effect in ‘hidden’ systems only accessible by scientists with specific tools and methods (e.g. changes in neuronal systems that the patients or therapist will hardly be aware of), but also in cognitive and functional outcomes that are observable and perceptible by those concerned. Otherwise the commitment of patients to participate and the therapists’ motivation to provide such trainings will be weak. While holding on to the basic principles of the neuroplasticity-based training, some parameters could be adapted: first of all, additional behavioral measures reflecting the neuronal mechanism of stimulus perception and differentiation should be added in future studies to exemplify the success of the training. Secondly, the training could be adapted in order to yield stronger and broader effects and thirdly, the duration of training could be extended (these suggestions are discussed in more detail in section 6.3).

It is vital to note that a specific computer-based training has to be incorporated in a broader therapy-plan and should never be offered as stand-alone treatment. Influences on and interactions with other therapy domains may be possible, yet hardly observable with scientific methods. In order to find out about the effects of training, the patient’s personal perspective has to be taken into account. The promising results of combining cognitive and social trainings (Hooker et al., 2012, 2013; Lindenmayer et al., 2012; Sacks et al., 2013) and of integrated psychological therapy (IPT) in schizophrenia patients (Roder et al., 2011) point in that direction. However, understanding the mode of action of the isolated components remains an important issue of research. The present thesis contributes to that goal by demonstrating the impact of a specific, auditory training program on the oscillatory activity in first-episode
patients (study three) and by adding evidence of the specificity of the training program (study four).

6.3. Limitations and outlook

The present study demonstrates that cognitive deficits and abnormal oscillatory dynamics in the auditory paired-click design in FE patients can be adjusted by training.

Strengths of the present project were the combination of measures used within one single study (neuropsychological and neurophysiological measures), the high number of assessments that were conducted (pre, post and follow-up) as well as the recruitment of a relatively rare patient sample (FE schizophrenia patients).

However, there were some limitations of the present study that should not be neglected:

A major problem of this study was the relatively small sample size that is particularly problematic in the light of the present heterogeneous sample. Small sample sizes are seen as a shortcoming of controlled clinical trials in clinical settings in general (Keefe et al., 2013). This problem may be even more difficult to overcome in FE, who are released faster than chronic patients and may be less committed to longitudinal studies.

First of all, FE patients are relatively rare. If the one-year prevalence for schizophrenia of 0.01–0.02% (Gaebel & Wölwer, 2010) is taken into account, one can easily calculate that in a city with the size of Konstanz (population about 85500) there will be on average no more than around 8–17 people newly diagnosed with schizophrenia per year (and they will not all seek help at the Center for Psychiatry Reichenau, where the patients of the present study were recruited). During our study there was no such thing as an early intervention program aimed at identifying people before the outbreak or at the beginning of psychosis in Konstanz, something that had been established in other cities (for example the ‘Früh-Erkennungs- & Therapie-Zentrum für psychische Krisen (FETZ)’ in Cologne or the ‘Projekt zur Früherkennung von Psychosen (fepsy)’ in Basel). Such programs make it easier to get access to patients as the institutions are consulted cross-regionally by them. Additionally to the challenge of recruiting FE patients, there were many dropouts in the present study, possibly due to motivational problems. Several reasons might account for this fact: as the term ‘first-admission’ or ‘first-episode’ implies, these patients often experience their first contact with a psychiatric setting at this point in time and they might be unfamiliar with the system as a whole. The diagnosis ‘psychosis’ or ‘schizophrenia’ can be a shock and the motivation and the capacity to take part in a research project may be limited. Also, at the early and often
acute phase of illness the positive symptoms – including mistrust – are sometimes relatively prominent, making it difficult for the patients to participate in parts of the study (especially the MEG session).

It can only be speculated that daily computer-based training within a neuroplasticity-oriented, rewarding context created more commitment and motivation (or perhaps curiosity if the cognitive problems – that many patients are aware of – really improve) than the normal inpatient environment. This would explain the larger number of dropouts in the TAU group compared to the training groups. Less incentive motivation has been observed in FE compared to healthy participants (Murray et al., 2008). Moreover, Nahum and colleagues (2014) and Fisher and colleagues (2014) emphasized motivation and (monetary) incentives as factors that modify training commitment and effects. For TAU, the lack of daily training appointments may have facilitated a loss of motivation to return for additional test and MEG assessments.

An additional limitation may have resulted from the duration of the training: in the present study, patients accomplished 20 training sessions whereas in other studies, participants were trained for 50 hours or even more (Fisher et al., 2009). In a meta-analysis by McGurk and colleagues (2007), a positive relationship between duration of treatment and outcome in verbal learning and memory was demonstrated. In the context of (acute) psychiatry and bearing in mind the characteristics of the present sample of FE patients, more sessions were hardly feasible although stronger effects might have been expected from longer training periods (e.g., Fisher et al., 2009, 2015; Hooker et al., 2014; Panizzutti et al., 2013). When developing a feasible training, one has to consider the reality in clinical settings (for example, there would probably not be enough clinical staff to coach 50–100 training sessions per patient).

Another issue was that an impact of medication on test performance and learning cannot be ruled out, although evidence for this is diverse: Vinogradov et al. (2009) report a significant association between serum anticholinergic activity, MCCB test performance, and cognitive training. Moritz et al. (2013) emphasize the dampening effect of antipsychotic mediation on test performance, while a meta-analysis (Fatouros-Bergman et al., 2014) could not substantiate such medication effects. In our study, no relationship between test-performance and amount of medication was found, although potential effects can only be studied by the direct comparison of drug-naïve with medicated patients.
Finally, it can only be speculated why the MCCB did not reveal any specific training effects but an improvement in cognitive functions independent of treatment in all patient groups. We could ask the same question as Green and colleagues (2000) did in their article of the same name: ‘Neurocognitive Deficits and Functional Outcome in Schizophrenia: Are we measuring the right stuff?’. The MCCB might not have been sensitive enough to display the specifically trained functions. It can be assumed that the patients improved their auditory processing as the training sessions were adaptive and all patients reached higher levels during the course of training without exception. Unfortunately, the training program did not allow us to save the data and to use it for further analysis. In another study from our lab, Popova (2014) could demonstrate distinct improvement for the facial affect recognition training in parameters more closely related to the trained functions.

There are still many research questions remaining that could not be addressed in the present thesis but that are relevant for future research.

First of all, in the current study we could not make any claims about the structural abnormalities in the present sample of FE patients. If neuroplasticity is defined as ‘the ability of the nervous system to respond to intrinsic and extrinsic stimuli by reorganizing structures, functions and connections’ (Cramer et al., 2011), it would be of great interest to investigate if there is a relationship of anatomical alterations with the demonstrated abnormalities in oscillatory dynamics and if these potentially existing structural abnormalities can be modified by neuroplasticity-based training. Also, schizophrenia can be seen from the perspective of the disconnection hypothesis that states that the illness can be understood in cognitive and pathophysiological terms as a failure of proper functional integration in the brain (Friston, 1999). In the present study we focused on more regionally specific deficits (group x training interaction or group differences between healthy controls and patients). However, this type of analysis does not reveal any insights into the functional integration or putative dysfunctional connectivity, as we did not look at interactions between different brain areas. An understanding of the development of the dynamically maintained and remodeled connectivity in the brain of schizophrenia might be essential for further understanding the illness (Friston, 1999). Studies have shown general and specific connectivity impairments in FE patients (e.g., Fornito et al, 2011) but whether these impairments can be modified remains to be seen.
7. References


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8. Footnotes

Footnote 1: Sensory gating refers to a phenomenon of cortical response suppression to the second of two identical stimuli presented in rapid succession. This attenuation is thought to reflect a brain mechanism inhibiting the processing of redundant information, thus protecting the processing of information already under analysis. Sensory gating abnormalities are seen as an early clinical symptom in schizophrenia and might be a correlate of hypervigilant behavior and problems in focusing attention during the illness (Freedman et al., 1987; Freedman et al., 2003). A common, non-invasive technique for measuring sensory gating is the paired (or double-) click design. In this design, the person hears pairs of two identical clicks (S1 and S2) that are typically presented with a 500 ms onset-to-onset interval and a variable, longer offset-to-onset interval (e.g. 7-9 seconds). Both stimuli typically evoke an electromagnetic response ~50 ms after stimulus onset, the P50. The S2-evoked P50/S1-evoked P50 amplitude ratio commonly serves as a measure of sensory gating. M50 is the MEG analog of the EEG P50.

Footnote 2: Articles refer to early-onset, first-episode, or first-admission patients, but most such samples are young adults, recruited shortly after their first hospitalization, undergoing treatment for a schizophrenia spectrum disorder. The term ‘first-admission’ is used here to represent such early phases and because the present sample is in fact first-admission.

Footnote 3: Sensory gating refers to a phenomenon of cortical response suppression to the second of two identical stimuli presented in rapid succession. This attenuation is thought to reflect a brain mechanism inhibiting the processing of redundant information, thus protecting the processing of information already under analysis. Both stimuli typically evoke an electromagnetic response ~50 ms after stimulus onset, P50. The S2-evoked P50/S1-evoked P50 amplitude ratio commonly serves as a measure of sensory gating. M50 is the MEG analog of the EEG P50.

Footnote 4: For three patients the precise number of admissions could not be verified from files because some of the prior admissions were at hospitals for which records were not
available. For these patients, careful diagnostic interviews confirmed illness duration > 3 years together with a minimum of 3 inpatient and/or outpatient treatment occasions

Footnote 5: Aus Gründen der Lesbarkeit werden im folgenden Bezeichnungen wie ‚Patienten‘ oder ‚Teilnehmer‘ für die weibliche und männliche Form verwendet.

Footnote 6: Die jeweilige Intervention erfolgte zusätzlich zum individuellen medikamentösen und sozialpsychiatrischen Behandlungsplan.

Footnote 7: Für die in diesem Bericht integrierten Fragestellungen wurden zwei zunächst unabhängige Studien kombiniert. Da die Untersuchung ersterkrankter Patienten primär dem Einfluss von akustisch-verbalem Training auf den weiteren Verlauf kognitiver Leistungsfähigkeit galt, wurden diese Patienten nicht dem Affektdiskriminationstraining zugewiesen.

Footnote 8: The MCCB (MATRICS Consortium Cognitive Battery, Nuechterlein et al., 2008; German translation authorized by MATRICS,, Harvey et al., 2010) covers seven domains of cognitive functions that have been shown to be impaired in schizophrenia, including processing speed, attentional vigilance, working memory, verbal learning, visual learning, reasoning, and social cognition. MCCB results directly comparing FE and chronic patients have been reported in Carolus et al. (2015) and results for chronic patients in Popov et al. (2015).

Footnote 9: Two spectral analyses examined training effects in the 0-600 ms window: One emphasized time resolution using a window with a fixed length of 250 ms in sliding steps of 50 ms, resulting in 4-Hz frequency steps, the other emphasized frequency resolution using a window with a fixed length of 1000 ms in sliding steps of 50 ms, resulting in 1-Hz frequency steps. The spectral analysis with high temporal resolution suggests that group differences with greater 8-12 Hz power decrease after BFP than after TAU become evident as early as 80-230 ms after S1-onset, (Group x Time, F(1,33) = 11.78, p < .01; Time, BFP, F(1,20) = 8.87, p < .01; TAU, F(1,14) = 4.03, p < .1). Both, early and late effects are related and do not indicate different processes.
Footnote 10: Current views of the “alpha” frequency range involve a larger range of frequencies than the traditional 8-12 Hz range. More recent results refer to alpha frequency windows 14-16 Hz (Mazaheri et al., 2014), 8-14 Hz (Haegens et al., 2014), 7-14 Hz (Spaak et al., 2012), 6-15 Hz (Weisz et al., 2014), or 8-16 Hz (Frey et al., 2014).

Footnote 11: Comparing effects of two specific training protocols benefits from testing effects using tasks that measure the specifically targeted versus non-targeted function. Such a group x task design was employed in the overall project. The present report evaluates intervention effects in the paired-stimulus task, whereas intervention effects on facial affect discrimination in overlapping patient samples and an overlapping healthy comparison sample are reported separately (Popova et al., 2014).

Footnote 12: FAT includes a series of visual exercises involving human face expression, two emphasizing facial affect discrimination and two emphasizing working memory. FAT was designed to be comparable to BFP in neuroplasticity-based learning, differing in the content of tasks. The same/different task trained the ability to discriminate whether two different posers express the same or different emotions, replacing the discrimination of two syllables/phonemes in the BFP protocol. The blended emotion task addressed the identification of a target emotion in morphed faces, which Popov et al. (2014) found to be impaired in schizophrenia patients: in order to train this type of affect discrimination, each face combined two 50/50 morphed facial expressions. The participant was asked to indicate which two emotions in an array of seven standard Ekman emotional expressions were combined in the presented face by clicking on the respective expression in the array of facial pictures. The emotion sequence task trained the recognition of the sequence of a series of facial affect expressions from a single poser per trial, corresponding to the BFP Training-induced modulation of oscillatory brain activity in schizophrenia 27 task of reproducing the sequence of a series of syllables/phonemes per trial. In the emotion location task, patients learned to recall the location of identical pairs of poser/emotion combinations among an array of hidden faces corresponding to the BFP task of recalling the location of identical pairs of syllables/phonemes that were acoustically presented upon touching the respective cards in an array. Emotional faces were obtained from the KDEF data bank (http://www.emotionlab.se/resources/kdef) and included male and female Caucasian faces.
expressing one of seven emotions (sad, happy, disgusted, fear, surprised, angry, neutral). Within each task, level of difficulty was adjusted to individual performance by increasing difficulty after 6 correct (non-consecutive) responses or decreasing difficulty after 3 consecutive errors. This algorithm ensured increasing difficulty with improving performance. Performance feedback was provided within session after 6 correct responses per level (the transition to the next level of difficulty) and at the end of each task. Performance on the four tasks was evaluated as the proportion of correct responses per level of difficulty for each task and each session. Performance change following FAT was evaluated by comparing scores for the first and the last sessions. The meaning of performance scores varied qualitatively for the different tasks. Therefore, change in performance scores was evaluated separately for each task, using dependent sample t-tests and effect size (Hedges’ g).
9. Supplements

Methods Supplement for:

Section 2: Functional cognitive and cortical abnormalities in chronic and first-admission schizophrenia.

Data Reduction and Analysis: Prior to correcting for heart and eye-blink artifact by means of independent component analysis, trials containing movement artifact or SQUID jumps were rejected based on visual inspection. Global noise was removed offline by subtracting external, non-biological noise recorded by 11 MEG reference channels. Offline treatment of the MEG signals was accomplished primarily with the MATLAB-based open-source signal processing toolbox fieldtrip (Oostenveld et al., 2011) complemented by in-house MATLAB functions. Epochs of 1000 ms before and 2000 ms after the first click (S1) of each trial were extracted from continuous recordings.

M50 Gating Ratio: Epochs extending 100 ms before and 400 ms after each click (S1 and S2) were scored using procedures described for an independent participant sample in Popov et al. (2011). All channels for epochs with amplitude >4000 fT in any channel were rejected. On average 95 artifact-free trials/participant were available, with no differences between patients and control subjects (chronic patients, CHR: 95.3±5.5; first-admission patients, FA: 93.6±9.8; healthy comparison participants, HC: 95.5±5.3; F<1). Artifact-free epochs were averaged and filtered with a 1 Hz (12 dB/octave, zero-phase-shift) to 45-Hz (24 dB/octave, zero-phase-shift) bandpass filter using BESA 6.0 (http://www.besa.de). Via visual inspection of all channels simultaneously for a given subject, each M50 was defined as the segment of the event-related magnetic field (ERF) within a time window 40 to 80 ms after each click onset as the largest amplitude preceding M100. Visual inspection of the ERF ensured auditory cortical activation, typical dipolar topographic distribution with ingoing and outgoing magnetic fields around superior temporal gyrus, and corresponding polarity reversal and topographic distribution opposite in direction to that of M100. Based on these sensor data, sources were estimated by fitting a pair of regional sources simultaneously in the left and right hemisphere for a 20 ms interval centered around each peak, respectively. Dipole fitting used information from all 148 magnetometers, as simulation (http://www.besa.de/updates/tools) indicated that just 10%–12% of the variance in the measured signal was explained by activity at sensors over the opposite hemisphere (see also
Popov et al., 2011). Only solutions exceeding at least 75% goodness of fit (mean ± SD 92.7 ± 4.5%) for sources located in superior temporal gyrus were considered for analysis. All participants met this criterion for S1. Three CHR did not meet this criterion for S2, so results are reported for 32 CHR, 31 FA, and 28 HC. Initial scoring was done by a trained lab assistant who was not blind to diagnostic group. Scoring for each subject was cross validated by an automatic peak-detection software that did not use group information and in addition, for approximately half of the sample, by a senior colleague blind to group and not significantly involved in the study.

Oscillatory Dynamics: Epochs extending from 500 ms before to 1000 ms after the first click were scored for power at selected frequencies after screening for artifact using the criteria presented above. Spectral analysis was computed for each trial using two different sets of tapers to maximize the sensitivity for effects in different frequency bands. For frequency bins from 1 to 40 Hz, a single Hanning taper with an overlapping sliding time window (in steps of 100 ms) and fixed window length of 500 ms was applied. For frequency bins beyond 40 Hz, slapian multitapers (discrete prolate spheroidal sequences) were applied to each segment. A set of 5 multitapers was used, resulting in a spectral smoothing of +/- 6 Hz. For illustration, resulting power estimates were averaged over trials for each participant. Relevant time-frequency windows were determined by applying a cluster-based, one-sided, independent-sample t-test with Monte Carlo randomization (Maris and Oostenveld, 2007) to the sensor data. This procedure effectively controls for multiple comparisons and allows the identification of sensor clusters with significant group differences in 3D in sensor space (time, frequency, and sensors). Clusters judged significant across 1000 randomizations had to consist of at least 3 contiguous sensors.

A frequency-domain adaptive spatial filtering algorithm enabling the dynamic imaging of coherent sources (DICS; Gross et al., 2001; Popov et al., 2011) served to estimate sources of activity that contributed to effects in source space. This algorithm uses cross-spectral-density matrices obtained from the data to construct a spatial filter optimized for a specific voxel. The time windows and frequency bands of interest for the source-space clusters were based on results obtained for sensor clusters. Source reconstruction was based on individual structural MRIs (available for 27 SZ and 21 HC) and on an affine transformation of an MNI-template brain (Montreal Neurological Institute, Montreal, Canada http://www.bic.mni.mcgill.ca/brainweb) to the subject’s digitized individual head shape (see
also Keil et al., 2010). Source estimates were registered to the individual anatomical images and subsequently normalized to a standard MNI brain for illustrative purposes and in order to calculate group statistics. Again, statistical group differences were tested applying the nonparametric permutation test. Voxel clusters in source space were identified as differentially active when group differences exceeded a threshold of significance at the 5% level after 1000 randomizations. The test statistic was defined as the sum of the t-statistics of the voxels within the respective clusters. All analyses were computed for HC vs. SZ and for CHR vs. FA.
Section 4: Neuroplasticity-based training modifies oscillatory dynamics in first-episode schizophrenia patients

Table 8 Cognitive test performance on the MCCB (Matrics Consortium Cognitive Battery) prior to (t1) and after (t2) targeted training with the Brain Fitness Program (BFP) or Treatment-as-usual (TAU) expressed as mean T-score for each MCCB domain.

<table>
<thead>
<tr>
<th>MCCB domains</th>
<th>BFP (n = 20)</th>
<th>TAU (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>t1</td>
<td>t2</td>
</tr>
<tr>
<td>PS M (SD)</td>
<td>34.2 (13.1)</td>
<td>41.1 (12.9)</td>
</tr>
<tr>
<td>Att M (SD)</td>
<td>35.5 (13.4)</td>
<td>38.8 (13.0)</td>
</tr>
<tr>
<td>WM M (SD)</td>
<td>44.4 (12.8)</td>
<td>48.5 (11.3)</td>
</tr>
<tr>
<td>VL M (SD)</td>
<td>44.1 (10.7)</td>
<td>49.1 (14.6)</td>
</tr>
<tr>
<td>VisL M (SD)</td>
<td>37.6 (16.2)</td>
<td>41.1 (12.0)</td>
</tr>
<tr>
<td>Reas M (SD)</td>
<td>42.5 (9.7)</td>
<td>44.8 (8.7)</td>
</tr>
<tr>
<td>SC M (SD)</td>
<td>44.2 (11.1)</td>
<td>48.0 (12)</td>
</tr>
<tr>
<td>OA M (SD)</td>
<td>34.3 (14.2)</td>
<td>41 (13.6)</td>
</tr>
</tbody>
</table>

Notes: M: Mean, SD: standard deviation; PS: processing speed; Att: attention; WM: working memory; VL: verbal learning; VisL: visual learning; Reas: reasoning and problem solving; SC: social cognition; OA: Overall score.