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Cognitive deficits in schizophrenia – specific patterns, neural correlates and remediation through training

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List of scientific publications included in this cumulative dissertation

I. Article

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II. Article

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III. Article

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1 INTRODUCTION

There is consistent evidence that cognitive impairment is a key symptom of schizophrenia (Green, Kern, Braff, & Mintz, 2000; Wilk et al., 2005). These impairments affect most if not all areas of cognitive functioning, leading some authors to suggest a generalized disturbance (Dickinson & Harvey, 2009; Dickinson, Iannone, Wilk, & Gold, 2004), although memory, attention and executive functions might be more strongly affected than other functions (Heinrichs & Zakzanis, 1998; Weickert et al., 2000). Nevertheless, there is no typical "schizophrenic profile" that would enable a clear diagnostic classification for a single patient.

Research on cognitive impairment in schizophrenia has been driven by many goals. Two of them are especially relevant for the following studies. First, there was considerable hope that research on cognition could provide a pathway to the neurophysiological disturbances underlying the illness. Since brain processes underlying cognitive functions like verbal memory or attention are better known than those related to symptom formation, they should be easier to define. Since the 1980s, cognition research has contributed significantly to theories addressing the pathogenesis of schizophrenia. Nevertheless, neither genetic research nor the neurodevelopmental hypotheses have so far been able to develop a causal pathway to cognitive deficits. A longstanding question regards whether a core deficit can be defined on a cognitive or neurophysiological level, which causally leads to the broad array of observed impairments. If one could trace down the broad cognitive impairment to a single underlying malfunction, it is hoped that schizophrenia would become much better understandable and treatable. Evidence for instability in information processing has emerged that might explain a basal dysfunction in patients with schizophrenia leading to various cognitive limitations and clinical symptoms (Rolls, Loh, Deco, & Winterer, 2008; Winterer et al., 2006).

Second, during the 1990s it could be clearly shown that cognitive impairment can be dissociated from other symptom dimensions such as positive and negative symptoms. Importantly, evidence has been accumulating that cognitive impairment is an important predictor for functional outcome. Thus, a new – clinically oriented – phase in cognition research has begun, which regards cognitive deficits as relevant symptoms that require treatment. Since existing treatment for schizophrenia has at best limited impact on cognition, it became clear that specific treatment for cognitive impairment is necessary for improving functional outcome. Aside from the development of new drugs, a strong emphasis is on psychological interventions to improve cognition. These interventions have been subsumed under the term cognitive remediation and have an increasing evidence base.

The aim of the present work was to link the basic science and the clinical approach introduced above. In study I we ask whether instability in information processing could be a core deficit of the illness. Importantly, we link these observations with a measure of work

capability, thus bridging the gap between basic science and clinical levels. In study II we extend the basic approach to address instability of information processing on a neurophysiological level and we search for indication of compensation strategies on this level shown by patients with relatively preserved cognitive functions. Finally, study III is based at a clinical level and addresses the question of which level of cognitive functioning should be primarily addressed by training interventions.

2 THEORETICAL AND EMPIRICAL BACKGROUND

The following section will provide a brief theoretical and empirical overview of schizophrenia and the implications of cognitive deficits, discussing the question of a core deficit. The focus is then directed towards the effects of cognitive training. After a description of the methodological approach used in the three studies, an overview of the research questions and the results obtained in these studies will be given.

2.1 Schizophrenia and cognition

When assessing cognitive deficits in patients with schizophrenia, it is important to rule out the effects of long-term illness or side effects of treatment that might be present in chronically ill patients. Therefore recent studies concentrated on patients after stabilization of their first-episode of schizophrenia. In all important neuropsychological domains even first-episode patients perform an average of 0.64 to 1.20 standardized mean differences (Cohen's d) below healthy control means, which means effect sizes in the medium to large range (Mesholam-Gately, Giuliano, Goff, Faraone, & Seidman, 2009). Another study reported an even larger general deficit of 1.5 standard deviations in first-episode patients relative to matched healthy controls, and – in addition to the general deficit - subtle relative deficits in memory and executive functions whereas language was relatively spared (Bilder et al., 2000). This study compared the more and the less impaired patients by doing a median split and found a difference in profile. The "high ability group" (mean deficit of –0.83 standard deviations relative to the comparison group) showed an additional relative deficit only on the memory scale whereas the "low ability group" (mean deficit of –2.22 standard deviations relative to the comparison group) showed additional deficits on the memory as well as the executive function scale. Although relative deficits like the ones just described are statistically significant, their clinical importance can be questioned, as their magnitude is small compared to the dominant generalized deficit (Bilder et al., 2000). Therefore it is important to emphasize that despite a restricted set of subtests that are even more impaired than others, a very broad and severe generalized cognitive deficit remains.

The National Institute of Mental Health, the largest research organization in the world specializing in mental illness, initiated the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) initiative in order to overcome obstacles to drug development for cognitive impairment in schizophrenia. One aim was to construct a consensus cognitive battery to provide a relatively brief evaluation of key cognitive domains relevant to schizophrenia. It was designed as outcome measure in registry trials for cognitive agents in schizophrenia and therefore needed to cover all necessary cognitive domains. The chosen seven domains are speed of processing, attention/vigilance, working memory, verbal

learning, visual learning, reasoning and problem solving, and social cognition (Kern et al., 2008; Keith H. Nuechterlein et al., 2008), see table 1. One study (Holmén, Juuhl-Langseth, Thormodsen, Melle, & Rund, 2010) found significant differences between patients with schizophrenia and healthy controls on every MATRICS domain except for social cognition, thus emphasizing the usefulness of the chosen domains and tests as well as the generalization of the deficit.

Table 1: The seven domains of the MATRICS consensus cognitive battery of tests

Cognitive Domain	Test	Description
Speed of processing	Category Fluency	Verbal fluency for animals (tested for 60 seconds)
	Brief Assessment of Cognition in Schizophrenia (BACS), Symbol-Coding	Writing numbers corresponding to nonsense symbols (for 90 seconds)
	Trail Making A	Connecting consecutive numbers arranged in random order
Attention/vigilance	Continuous Performance Test, Identical Pairs (CPT-IP)	Monitoring numbers and responding when 2 digits in a row are identical
Working memory	Verbal: University of Maryland, Letter/Number Span	Mental reordering of an orally presented list of letters and numbers
	Nonverbal: Wechsler Memory Scale (WMS) III Spatial Span	Remembering the location of blocks pointed at in a certain order, repeating this order forwards and backwards
Verbal learning	Hopkins Verbal Learning Test (HVLT) Revised	A list of 12 words repeated three times
Visual learning	Brief Visuospatial Memory Test (BMVT) Revised	Six geometrical figures are displayed (for10 seconds), three times altogether
Reasoning and problem solving	Neuropsychological Assessment Battery (NAB) Mazes	Solving of seven mazes presented in increasing difficulty
Social cognition	Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT) Managing Emotions	Two subtests: Social Management asks how participants manage the emotions of others, Emotion Management asks how a person would regulate his or her own by giving examples for emotion regulation in a hypothetical situation

While the original descriptions of schizophrenia emphasized a progressive “dementia praecox”, recent research suggests that the cognitive deficits are relatively stable over time (Addington, Saeedi, & Addington, 2005; Heaton et al., 2001; Rund, 1998). Further it has been shown that cognitive deficits are not due to chronicity, medical treatment or institutionalization (Mohamed, Paulsen, O'Leary, Arndt, & Andreasen, 1999) nor sufficiently treatable by antipsychotics (Harvey & Keefe, 2001; Roesch-Ely, Pfueller, Mundt, Müller, & Weisbrod, 2010). Cognitive deficits are not restricted to the occurrence of schizophrenic symptoms but – especially in tests requiring executive functions (Snitz, MacDonald, & Carter,

2006) - also present to some degree in healthy relatives (Hilti et al., 2010; Trandafir, Méary, Schürhoff, Leboyer, & Szöke, 2006). They are also found in ultra high risk groups (Niendam et al., 2006; Seidman et al., 2006), and in patients later diagnosed with schizophrenia before their first psychotic episode (Caspi et al., 2003; Woodberry, Giuliano, & Seidman, 2008). Whether the duration of untreated psychosis affects the severity of cognitive deficits is discussed controversially, some studies did not find an association (Goldberg et al., 2009; Hoff et al., 2000; Norman, Townsend, & Malla, 2001; Rund et al., 2007; Rund et al., 2004) or only a very small one (Ho et al., 2003), others did (Amminger, Edwards, Brewer, Harrigan, & McGorry, 2002; Lappin et al., 2007). But even when an association was found, the question of causality could not be answered. All this emphasizes the difficulty to influence cognitive symptoms adequately.

Although approximately 20 to 25% of all patients with schizophrenia show neuropsychological test results in the normal range (Palmer, Dawes, & Heaton, 2009; Palmer et al., 1997), it is not clear whether they are completely unimpaired compared to their premorbid level of functioning or whether they still show some impairment but do not fall into the below-average range due to their excellent premorbid intellectual ability. The existing studies suggest that cognitive decline begins long before the first acute psychotic episode (Bilder et al., 2006), which renders it difficult to estimate the unimpaired level of premorbid cognitive functioning. And without an estimation of the unimpaired premorbid cognitive performance it is not possible to answer the question of cognitive decline or cognitive stability.

Giving a summary on the importance of cognitive deficits in schizophrenia is not possible without mentioning the link between cognition and functional outcome after remission. But as this aspect is of utmost importance, it is described in an extra section under 2.4., together with other aspects of everyday functioning in schizophrenia.

2.2 Is there a core deficit?

One major research goal concerning cognition in schizophrenia is to provide a pathway to a “core deficit” of the illness. The term “core deficit” has been used lavishly in schizophrenia literature, albeit being ill defined. The basic idea is to define a cognitive or neurophysiological disturbance, which can explain most - if not all - clinical features of the illness. To cause further confusion, the term is not only used in order to explain the disorder in a causal way, but some researchers simply use it to emphasize the significance of the specific deficit described by them. In the last years the term has been applied to a growing number of cognitive deficits, as cognitive impairment has been increasingly regarded as a core deficit of schizophrenia itself. Different core deficit candidates have been suggested: working memory (Gold et al.; Silver, Feldman, Bilker, & Gur, 2003), episodic memory (Ragland et al., 2009),

higher order hierarchical processing (Krishnan, Fivaz, Kraus, & Keefe), attention (Li et al., 2002) and executive functioning (Rüsch et al., 2007), or sensomotory gating (Potter, Summerfelt, Gold, & Buchanan, 2006). This diversity of possible core deficits is not astonishing, given the diversity of the disorder itself. And a core deficit is supposed to explain it all – the cognitive and the clinical symptoms alike.

Heterogeneity not only explains why the search for a core deficit is so intriguing, it also makes it harder. There are no unambiguous signs or symptoms. Even in the neurocognitive domain no clear "profile" could be established. All cognitive domains seem to be somewhat impaired with no obvious hint towards one main deficit. Partly this has to be expected, as most neurocognitive tests measure more than one concept (Dickinson & Gold, 2008). For example it is hard to design a test that does not require a minimum of attention or working memory, and a lot of tests have a speed component. As a consequence the question arises, whether the proposed single underlying deficit (Keefe et al., 2006) might just be a measurement artefact, consisting of the overlap between only seemingly independent tests.

Nevertheless, there are indications that there is one common factor underlying the cognitive deficit (Keefe et al., 2006) and that relatively few tests are necessary to assess this deficit. Instead of various cognitive domains measured by several tests, it could be sufficient to rely on a couple of tests – if one knew which the essential ones are. The concept of one or a few "core deficits" could not only help to simplify the diagnosis but also to understand better what causes and influences the process of the disorder. But despite growing effort, the search for a common factor underlying schizophrenia in its changeable manifestation is still going on.

But even if there is a core deficit – there are so many candidates and they are so hard to separate, so where to start the search? Given that there is a general impairment, it seems hard to advance it towards narrowing down the long list of cognitive deficits to the more severe and fundamental ones when searching in a population of chronically ill patients. A new idea has emerged that proposes to concentrate on a high-functioning subpopulation of patients with schizophrenia. Because not all schizophrenic patients show severe cognitive deficits compared to healthy controls or compared to their own estimated premorbid IQ (Heinrichs et al., 2008; Kremen, Seidman, Faraone, Toomey, & Tsuang, 2000, 2004; Palmer et al., 1997), it could be helpful to concentrate on these patients. The small deficits that still can be found in this population could be essential for the understanding of the disorder. As the deficits still present in a high-functioning patient group compose what can be called a core deficit, they may be more important targets of intervention than other deficits. And when core deficits have been identified, in a further step it might be possible to analyze whether theses deficits really lead to the various additional cognitive deficits and symptoms present in

more severely impaired patients, or whether some part of the broad impairment is composed of independent deficits.

This approach can be seriously criticized, as another possibility would be that the non-impaired patients belong to another sub-group of schizophrenia than the cognitively impaired patients (Ammari, Heinrichs, & Miles, 2010; Cascella et al., 2008). This would mean that their core deficit could be a different one, leading not only to less further cognitive impairment in this subpopulation but also to qualitatively different impairments and symptoms.

We assume that the sub-group of relatively unimpaired patients of schizophrenia does not consist of a specific diagnostic group but might have reached their near to normal cognitive performance due to compensation on a neurophysiological level. Effective compensation could for example be achieved by training or by good premorbid functioning. There have been reports of differences between groups of “high-functioning” patients and patients with the typical cognitive deficits, but no clear description of subgroups emerged over several studies. One study did not find differences in severity of positive and negative symptoms between verbally superior and verbally impaired patients with schizophrenia (Heinrichs et al., 2008). In another study no differences in cognitive processing speed in comparison to more cognitively impaired patients with schizophrenia could be found (Badcock, Dragovic, Waters, & Jablensky, 2005), which could be interpreted as a hint towards the same underlying impairment. Even the whole concept of being “neuropsychologically normal” while suffering from schizophrenia was doubted (Wilk et al., 2005), as subtle deficits can still be found. Therefore, the idea of a distinct subgroup is not proven yet and we assumed the idea of cognitive deficits occurring on a continuum. We speculated that concentrating on patients with near to normal cognitive performance would enable us to find out whether intra-individual variability is a viable core cognitive deficit candidate. In addition, a high-functioning patient group would enable the search for neurophysiological compensation strategies, as it can be assumed that a good cognitive performance despite a neurophysiological deficit could only be achieved by compensation.

2.3 Schizophrenia and variability

If there is a core deficit, it should affect nearly every cognitive process, especially memory, attention and executive functions. It therefore has to be a basal dysfunction that cannot easily be compensated or avoided. Probably it interrupts cognitive processes on a neurochemical or neurobiological basis (Dickinson & Harvey, 2009; Rolls et al., 2008).

Winterer (Winterer et al., 2006) assumed increased noise in frontal cortical networks in schizophrenia, which would lead to distorted information processing. The proposed decrease in signal-to-noise ratio would also lead to unreliable and unstable electrophysiological responses of prefrontal cell assemblies. This instability on a neurophysiological level in turn

would result in higher intra-individual variability (IIV) of reaction times on a behavioural level. Increased IIV could be the cause of further cognitive deficits, as it would go along with an unstable performance or with higher error-rates. Therefore Wexler (Wexler & Nicholls, 2004) supposed IIV to play a leading role in understanding cognitive deficits in schizophrenia and in differentiating them from cognitive deficits found in patients with other diagnoses. If increased noise in cortical networks does exist, it should have effects on behavioural data in making reaction times more “noisy” or more variable. One way of checking this assumption is to analyze dispersion of reaction time data.

Research on reaction time data of patients with schizophrenia has a long tradition. It is a well-known fact that patients show prolonged reaction times in most tests (Keith. H. Nuechterlein, 1977). Slowing down in motor tasks as well as information processing was one of the first well-documented cognitive deficits of patients with schizophrenia. However, speed is not the only relevant parameter; variability of reaction times contains essential additional information. Therefore the observation that patients with schizophrenia show increased IIV in their responses when performing simple tasks is nearly as old as the knowledge about reaction time slowing itself. However, this observation has rather been interpreted as a consequence of slowing than as an independent and important deficit and has thus been considered to be of relatively little interest. Now the theoretical background of increased cortical noise leads to the hypothesis that increased IIV might be more than a side-effect of general slowing – it might even be the main deficit. That explains why an old branch of schizophrenia research that seemed to offer no new prospects is now revived and broadened.

Variability can be assessed from different measures, ranging from compound measures like intelligence quotients to simple reaction times. According to Stuss et al. (Stuss, Pogue, Buckle, & Bondar, 1994) different forms of variability describe different phenomena. They propose three different kinds of variability: 1.) *„diversity“*, meaning variations within one group of subjects, or inter-individual variability, 2.) *“dispersion”*, meaning variations within one individual, or intra-individual variability, 3.) *“consistency/stability”* meaning variations within one subject over several measurement points, or time-dependent variability. Patients with schizophrenia show increased variability in all three measures. Nevertheless, the variability Winterer suggested that reflects the underlying neurophysiological instability is the second form, “dispersion”. This kind of variability should allow a better understanding of problems occurring within one patient within a limited time-frame, as it normally happens during one neuropsychological test.

IIV of reaction time has several advantages over conventional neuropsychological measures like mean errors and mean reaction time. It not only concentrates on the central tendency of performance, it also takes into account dispersion as additional information.

Therefore the time-dependent course of performance can be analysed and stability can be assessed.

This is not just one additional piece of information, but a measure that might be highly relevant for everyday functioning as well. It seems plausible that for everyday tasks like an eight hour work day, it is not only the best performances delivered within a short time that count, but the patients need to perform their assignments with a certain stability and continuity. Besides the work context, stability of functioning seems essential for social tasks as well. It can be imagined that for social partners it is very irritating when patients seem to follow a conversation closely at one moment but seem to be completely lost at the next. A clearly assessable and predictable small deficit might be easier to deal with than the fluctuation between normal functioning and a considerable but incalculable deficit. Despite this consideration, the link between IIV and everyday functioning has only been addressed in one study (Wexler & Nicholls, 2004). In this study a negative correlation between IIV of reaction times and hours as well as quality of work was reported. Consequently it would be possible to estimate a complex and highly relevant behaviour at work by a simple and easily obtainable measure like the IIV. Unfortunately the study has severe limitations because of its small sample size and its mixture of dispersion and consistency. Furthermore, the study was only reported in the form of a letter to the editor, therefore lacking information about the assessment of work performance. Nevertheless it showed that the association between IIV and everyday functioning – especially work performance – might be a rewarding field of research.

Besides the highly relevant additional information concerning stability of performance, IIV might help to show even minor cognitive deficits that are present in patients that show little deficits otherwise. IIV seems to be a very sensitive measure, depicting fluctuations in reaction time when mean reaction time measures seem unimpaired. At least this has been the case in comparisons between patients with ADHD and healthy controls (Klein, Wendling, Huettner, Ruder, & Peper, 2006) as well as between non-impaired traumatic brain injury patients and controls (Collins & Long, 1996).

Only recently IIV has become the focus of event-related potential (ERP) or imaging studies. The analysis of single-trial ERPs has lead to the conclusion that schizophrenic patients vary more in their P3 component (Ford, White, Lim, & Pfefferbaum, 1994; Roth, Roesch-Ely, Bender, Weisbrod, & Kaiser, 2007). But as the P3 emerges after the execution of the motor response, the cause for higher IIV in motor reaction times has to be searched even earlier in information processing.

An association between higher latency variability of the P3 and accuracy of task performance has been found (Roth et al., 2007), with patients characterized by more variable P3 components showing a more deficient task performance. Therefore the question arises

whether patients showing normal task performance still show higher temporal variability in their electrophysiological components and – if so – whether high-functioning patients show additional electrophysiological activation in areas normally not activated in order to compensate for the loss of effectiveness due to increased IIV.

2.4 Schizophrenia and everyday functioning

One reason why cognitive deficits increasingly draw the attention of researchers is their implication for the "functional outcome" of patients (Brekke, Hoe, Long, & Green, 2007; Green, 1996; Green et al., 2000), which means everyday functioning in the society. This general notion has been confirmed in numerous studies reflecting a variety of settings and outcome measures. Improvement during rehabilitation is limited by cognitive deficits (Bell & Bryson, 2001; Bell, Tsang, Greig, & Bryson, 2009; Brekke, Hoe, & Green, 2009; Kurtz, 2011). Cognitive functioning seems to be a good predictor for functional outcome after remission (Bryson & Bell, 2003) especially for employment (Tsang, Leung, Chung, Bell, & Cheung, 2010). These findings have driven the growing interest in understanding and influencing cognitive deficits. For example, one study (Bell, Tsang, Greig, & Bryson, 2007) found logical memory to be the only significant predictor of symptom improvement during 13 to 26 weeks of work therapy. In a review a link between change in cognitive function and change in functional outcome was found (Matza et al., 2006), although the authors emphasize that due to inconsistencies, the results are preliminary.

As everyday functioning consists of many different abilities and aspects, it is hard to assess. The general idea is to find measures of coping with everyday challenges in different areas of life. There are different concepts and frequently used terms how to describe or summarize what can be understood as "social outcome'": standard of living, quality of life, social integration, social adaptation, social functioning, or needs for care (Priebe, 2007). In other studies, the "social outcome" is simply measured by working hours. It is problematic that there is no universally accepted definition for any of these concepts and each can be used and assessed in different ways. But although there is no uniform definition, the problems patients with schizophrenia encounter in everyday functioning are considerable and not limited to one specific effect – therefore they have been found no matter which concept was applied.

Easily observable problems in everyday functioning are connected to employment. Most patients are not able to support themselves with their earnings, they work in sheltered workshops or low-qualified jobs – if they have an occupation at all (Marwaha et al., 2007). In the European literature employment rates between 10 and 20% are reported (Marwaha & Johnson, 2004). Generally people suffering from severe mental illness have a socio-economical disadvantage (Dohrenwend, Levav, Shrout, & Schwartz, 1992). As a whole,

patients are less well-educated than the average population, which can be explained by the early onset of the disorder, with the prodromal phase often starting before education having finished, especially for males. Additionally, patients show a constant downward drift in society and have a relatively high risk to become a social drop-out (Aro, Aro, & Keskimäki, 1995).

This fact leads to another important aspect besides work: social contacts. Even at the beginning of the disorder or before their first episode, the social networks of people later diagnosed with schizophrenia are characterized by reduced size, a high proportion of family members, and the dense interconnections among network members. These characteristics remain relatively stable (Horan, Subotnik, Snyder, & Nuechterlein, 2006). A large proportion of patients with schizophrenia stay single (Thara & Srinivasan, 1997) although their subjective quality of life estimation is linked to marital status in a positive way (Kovess-Masféty et al., 2006). In summary, work and relationships are two important areas of life affected by the disorder.

Following the acute psychosis, a relatively large proportion of patients suffer from persistent negative symptoms, which in combination with the cognitive deficits hinder the return to an independent life. Some patients even need help in their daily routine, they live in asylums or assisted living and need long-term care to a differing degree. For that reason, even to maintain a structured day is a challenge – let alone keeping up social networks, finding a partner, finishing education or starting an occupational re-training. All these negative effects lead to a lower quality of life, but it is hard to describe exactly how the different symptoms and deficits interact with each other. Nevertheless, it could be shown that cognition is related to other variables of interest: Besides disorganized (van der Does, Dingemans, Linszen, Nugter, & Scholte, 1996) and negative psychotic symptoms (Basso, Nasrallah, Olson, & Bornstein, 1998; Bozikas, Kosmidis, Kioperlidou, & Karavatos, 2004; Schuepbach et al., 2004) cognitive deficits are associated with subjective quality of life (Mohamed et al., 2008). Cognitive performance therefore plays an important role in the lives of patients, especially after subsidence of positive symptoms.

Given the pronounced deficits that accompany cognitive impairment and negative symptoms alike, it was a matter of time when it was tried to find one model to explain the effects of both on functional outcome. For an observer it is often hard to tell whether tasks are impeded by negative symptoms or by cognitive deficits. Therefore, the relationship between these domains has been analysed in several studies. At first, only the importance of cognitive deficits for the functional outcome was emphasized (Green, 1996; Harvey, Green, Keefe, & Velligan, 2004; Harvey, Koren, Reichenberg, & Bowie, 2006; McGurk, Mueser, Harvey, LaPuglia, & Marder, 2003; Shamsi et al., 2011; Ventura, Hellemann, Thames, Koellner, & Nuechterlein, 2009). But soon, negative symptoms were found to have an

important influence on functional outcome besides cognitive deficits (Milev, Ho, Arndt, & Andreasen, 2005). Meanwhile it is assumed that their role might at least partially be that of a mediator between neurocognition and functional outcome (Brekke et al., 2007). As cognitive deficits lead to impaired social competence as well, models have been extended by social cognition as an additional variable to explain more variance of the functional outcome.

2.5 Schizophrenia and cognitive training

As mentioned above, cognitive deficits clearly limit the possible functional outcome of patients with schizophrenia. Although other factors have an influence on patients' functional outcome as well, cognitive deficits have consistently been found to be a strong predictor. Gold (Gold, 2004) emphasizes that cognitive deficits are an ideal target for therapeutic intervention, as they are a well-documented, broad, frequently occurring symptom that is stable over time and relatively independent from psychopathology. Furthermore, cognitive deficits are neither easily nor sufficiently treated by medication (Roesch-Ely et al., 2010) and interfere with other possible limiting factors as well, as they may impede a process of rational analysis and problem solving for more complex aspects of social or functional outcome. Therefore cognitive training seems to be a necessary first step for further therapeutic interventions, especially cognitively demanding ones.

In turn, this leads to the idea that an extensive and adaptive cognitive training should enable patients to deal with potential problems in their daily life more successfully (Bellack, Dickinson, Morris, & Tenhula, 2005). As cognitive deficits become less severe, it should be easier for patients to focus on a problem and to apply their restored problem solving abilities to important areas of vocational and social life. Therefore cognitive trainings are becoming more and more important in clinical practice. The scope of aims and methods has considerably expanded in recent years (Wykes, Huddy, Cellard, McGurk, & Czobor, 2011).

Cognitive training initially was designed for neurological patients and only later was adopted for cognitive remediation of patients with schizophrenia. Cognitive training or cognitive remediation is an umbrella term used for a variety of methods to enhance cognitive functioning. Methods differ in terms of the medium (paper and pencil exercises, computer based training), training duration and intensity, group size and availability of professional help as well as the focus on "drill and practice" versus the acquisition of new compensatory strategies (McGurk, Twamley, Sitzer, McHugo, & Mueser, 2007). Only recently it was emphasized that patients with schizophrenia for the most part have limited insight into their cognitive deficits, which might limit their motivation for cognitive training (Medalia & Thysen, 2008). Therefore another important aspect of cognitive training interventions should be how motivation is enforced and interest in the training task is aroused.

Meta-analyses of cognitive trainings have found effect sizes in the moderate range for studies of generalization from the task that was used for training to independent measures of neuropsychological functioning or daily functioning (Grynszpan et al., 2010; Krabbendam & Aleman, 2003; McGurk et al., 2007; Twamley, Jeste, & Bellack, 2003). Surprisingly, the number of hours a training took place was not related to the improvement in overall cognitive functioning (McGurk et al., 2007), so even short interventions seem successful. On the other hand, treatment intensity was found to have a significant effect (Medalia & Richardson, 2005). In a recent study, cognitive training even had a positive effect on patients' quality of life, although it was embedded in a standard rehabilitation programme and therefore not the only intervention (Cavallaro et al., 2009). The most recent and extensive meta-analysis of cognitive remediation found an effect size of d=0.45 for global cognition and d=0.43 for durability of treatment effects on global cognition (Wykes et al., 2011). The authors emphasize that the functional outcome is optimized by combining cognitive remediation with other rehabilitation programs, especially if strategy teaching is used rather than drill and practice alone. They assume that in this case, transfer of cognitive training to relevant daily tasks is supported. It seems promising not only to practice cognitive abilities in an abstract setting and to hope that patients are able to make use of their new skills in everyday life but to search for cognitive training tools that offer a more realistic setting and to explicitly discuss transfer possibilities with patients.

Most of the training effects seem relatively stable one year after the end of the intervention (Bell, Zito, Greig, & Wexler, 2008; Hogarty, Greenwald, & Eack, 2006), but it has to be emphasized that Bell's cognitive training took part for 12 months and Hogarty's patients received training for two years. Eack and colleagues (Eack, Greenwald, Hogarty, & Keshavan, 2010) also could show that the improvement brought about their extensive two-year lasting training remained constant one year after the end of training. In one study the training only lasted for 3 months and therefore is more relevant to short-time interventions achievable in normal inpatient treatment. In that study cognitive performance at a follow-up three months after the end of training showed that most of the training-induced positive changes had lasted (Twamley, Savla, Zurhellen, Heaton, & Jeste, 2008). In one study the training was completed after approximately 12 weeks of training. Six month later the authors still found durable improvements in working memory (Wykes et al., 2007). If long-term effects of short interventions will be confirmed in further research, cognitive training could actually show the potential to save costs because of its effect on the vocational functional outcome (Patel et al., 2010).

Most of the time cognitive trainings are part of a more comprehensive treatment and no single intervention. This enables patients to use their restored cognitive skills in other settings as well and to practise them in natural environments. Therefore the concept of

"synergy" has been suggested (Bell & Bryson, 2001), as cognitive training alone might not achieve a generalisation to everyday functioning. That is why their "neurocognitive enhancement therapy" (NET) includes not only a training on the computer but feedback on cognitive performance at work as well. Other prominent examples like "Integrated psychological therapy" (IPT) by Brenner and colleagues (Brenner et al., 1994) or "Cognitive enhancement therapy" (CET) by Hogarty and Flesher (Hogarty & Flesher, 1999) try to integrate cognitive and social aspects in their programmes as well.

Nevertheless, the ingredients of the most successful cognitive remediation still remain somewhat speculative, and the interaction of training characteristics with special patient characteristics like age or motivation are far from clear. As Wykes and Huddy have pointed out, there is still little evidence for the superiority of any treatment approach, and meanwhile there are many available (Wykes & Huddy, 2009).

2.6 Research questions

Schizophrenia research works on different levels, from neurophysiological disturbances underlying the illness to everyday functioning. Often research focuses on one level and ignores the others in order to reduce complexity. Only recently associations between levels like performance in cognitive tests and performance in the real world have explicitly been addressed. In doing so, the two research aims of cognitive functioning in schizophrenia mentioned in the introduction can be pursued more effectively: understanding the core deficits of the disorder on a neurobiological level on the one hand and developing adequate interventions which improve the functional outcome most effectively on the other hand.

It is one main goal to find the best intervention strategies to improve cognitive functioning, as deficits in psychosocial functioning still are not treated sufficiently despite all progress in pharmacology and therapy. It is therefore another main goal to understand what mechanisms lead to the cognitive deficits that still limit the effect of most interventions and what exactly might be the core of the deficit.

The following studies try to analyze the association between the neurophysiological level, the cognitive performance level and the level of functioning at work in order to develop an explanation of patients' observable everyday difficulties through the underlying neurocognitive deficits. The three studies not only link the different levels but also follow two important goals of psychological research relevant for cognitive deficits in patients with schizophrenia. They cover cognitive deficits as a pathway to understanding illness mechanisms and cognitive deficits as separate treatment targets.

In the first study we hypothesized that increased IIV caused by higher cortical noise might be an underlying neurocognitive deficit which is present even in high-functioning patients with schizophrenia and shows malfunctioning although other cognitive tests are in the normal

range. It was further assumed that this deficit could be assessed by higher IIV in reaction times and would correlate with a measure of everyday functioning.

In the second study it was hypothesized that increased IIV can be shown with EEG using single-trial analysis, thereby demonstrating that variability can be shown on an electrophysiological level. It was further hypothesized that additional brain regions are recruited to compensate for the neurophysiological instability reflected in the temporal IIV.

The third study was concerned with the possibility to improve cognitive functioning and as a result everyday functioning by computer-assisted cognitive training. It was hypothesized that a training program focussing on problem solving would be more efficient in generalizing to improved everyday functioning than a training program focussing on basic cognitive abilities, because it employed a more realistic training task and focussed on transfer of strategies to the real world.

In the next section, the methods applied will be briefly introduced and the three studies will be summarized in more detail with special emphasis on the main outcomes and the implications for the understanding of cognitive deficits in schizophrenia.

3 GENERAL METHODS

3.1 Experimental paradigm: Go/Nogo task (studies I & II)

Go/Nogo tasks are simple reaction time tasks that demand attention and especially inhibition (Drewe, 1975; Eimer, 1993; Kaiser et al., 2006). These tasks can be varied for different parameters and result in a high number of trials without taking much time. The Go/Nogo task comprises of two different sets of stimuli: One requires a response (normally a button press, sometimes only counting), one has to be ignored. Go/Nogo tasks are often used in electroencephalogram (EEG) studies, as they allow comparisons between the trials requiring a response and the trials requiring inhibition of a motor reaction, leading to specific components in the event-related-potentials associated with inhibition.

We used a visual Go/Nogo task without a warning cue. Subjects were required to answer as fast and correctly as possible by pressing the left mouse button to a visual target stimulus (e.g. a square). To a second non-target visual stimulus (e.g. a circle), no reaction was required. The task was divided into two halves (runs), separated by a short break so that subjects could rest. In each of the two runs, we used a mixed sequence of 4 Go and 4 Nogo blocks of 40 trials, At the beginning of each block, probands were informed whether the target would occur infrequent (Go-condition) or frequent (Nogo-condition).

In the infrequent target condition the stimulus requiring response occurred in 20 percent of trials. As the challenge of this task lies in detecting the infrequent targets and implementing the required response, we called it the “Go”-task. In the frequent target condition the stimulus requiring response occurred in 80 percent of trials. As the challenge was to inhibit this prepotent response in the remaining 20 percent of trials, we called it the “Nogo”-task. In one trial the stimulus was presented for 132ms followed by a fixation cross for 1376ms. The sequence of trials within each block was pseudorandomized and no more than two rare events occurred in direct sequence.

3.2 Intra-individual variability of reaction times (study I)

There is more than just one method to measure IIV and results regarding variability can differ depending upon the measure chosen. Therefore a brief overview about some of the more or less common methods to measure IIV is provided.

3.2.1 Conventional measures

Although it is known that reaction times are not normally distributed, one conventional measure often provided as additional information to the mean reaction time is the intra-individual standard deviation (ISD). It has the advantage of being understandable and easily calculated, often even being part of the automatically displayed output when computer tests are applied. But as longer reaction times are correlated with increased variability, the measure is biased.

Therefore it has been recommended to rather calculate the intra-individual coefficient of variance (ICV), which means dividing ISD by the individual mean reaction time (Wagenmakers & Brown, 2007). A larger ICV still means more variability, but in relation to the own reaction time. It is a standardized measure with the advantage of correcting for the higher variability due to slowness. However, its use has also been critically discussed, as it depends on the linear relationship between mean and standard deviation of reaction times (Wagenmakers & Brown, 2007).

3.2.2 Ex-Gaussian distribution

In a critical article regarding the interpretation of the ex-Gaussian distribution, Matzke and Wagenmakers (Matzke & Wagenmakers, 2009) explain the history of distributions used to model reaction times. They summarize that the ex-Gaussian came up after it was realized that mean reaction times are not sufficient in describing the whole information that is inherent in reaction time data and that reaction times are not normally distributed. The ex-Gaussian distribution results from the convolution of a Gaussian and an exponential distribution. It is defined by three parameters: μ (the mean of the Gaussian component), σ (the standard deviation of the Gaussian component), and τ (the mean of the exponential component). The ex-Gaussian distribution has a positively skewed unimodal shape and if one looks at the probability density distribution, μ and σ reflect the ascending curve and τ reflects the tail of the distribution. Therefore τ would be the parameter that increases considerably if the tail of the distribution is larger due to a higher amount of quite slow responses.

Although it has been criticized that the ex-Gaussian distribution lacks a theoretical basis it nevertheless produces an excellent fit to empirical reaction time distributions. It therefore can be used as a descriptive distribution of reaction time data, whereas the idea that certain cognitive processes (like drift-rate) correspond with certain parameters has not been confirmed yet.

3.3 Intra-individual variability of event-related potentials (study II)

Given the assumption that intra-individual variability may play an important role in causing cognitive deficits in schizophrenia, it should not only be found in reaction times but in neurophysiological measures at well. The challenge is to find a way of assessing this variability. One attractive solution using EEG data involves single trial analysis and shall be introduced briefly.

3.3.1 Electroencephalography and event-related potentials

Although functional magnetic resonance imaging (fMRI) has improved immensely in the last years and is used intensively in research, in questions mainly interested in the time domain of information processing, electroencephalography (EEG) still is the better option. Electrical activity is measured at the scalp at different electrodes. In contrast to fMRI it directly reflects electrical activity in neuronal cell assemblies (Gazzaniga, Churchland, Sejnowski, Hillyard, & Raichle, 2000).

According to Picton and colleagues (Picton et al., 2000) event related potentials (ERPs) are “voltage fluctuations that are associated in time with some physical or mental occurrence”. Which means that ERPs are caused by some internal or external trigger and are supposed to follow a stimulus in the same sequence of positive and negative voltage changes every time. ERPs are generated by averaging electroencephalogram (EEG) data which records cerebral activity from the scalp, over a large number of trials for the same stimuli. This is done to average out random electrical activity that is not linked to the stimulus and to obtain a curve that shows only information processing related to the stimulus.

An interesting event-related potential that can be observed in Go/Nogo tasks is the N2. This negative wave peaks between 200 and 350 ms after stimulus onset (Folstein & Van Petten, 2008) at fronto-central electrodes, especially in the Nogo task. This component has been long said to be caused by the inhibition of a prepotent motor response (Falkenstein, Hoormann, & Hohnsbein, 1999; Jodo & Kayama, 1992) or the inhibition of the motoric preparation of the said response (Zordan, Sarlo, & Stablum, 2008). Later it was suggested that the N2 was a component associated with conflict monitoring (Gajewski, Stoerig, & Falkenstein, 2008) or cognitive control in general (Nieuwenhuis, Yeung, Van Den Wildenberg, & Ridderinkhof, 2003). Reduced N2 amplitude is a robust abnormality in patients with schizophrenia present in a variety of tasks (Brown, Gonsalvez, Harris, Williams, & Gordon, 2002; Bruder et al., 1998; Egan, Duncan, Suddath, & Kirch, 1994; O'Donnell et al., 1993; Umbricht, Bates, Lieberman, Kane, & Javitt, 2006).

3.3.2 Single trial analysis

Single trial analysis is a special procedure in EEG analysis used for more precise descriptions of electrical activity in the brain. Comparable to mean reaction time which is important but lacks information by ignoring the variability, ERPs simplify the real-time data by averaging all trials using the onset of the stimulus as reference point. Averaging assumes that information processing sequences follow exactly the same course of time for every trial. However, averaging would not only get rid of unwanted noise and artefacts but of parts of the "real-time" data as well. Even considering healthy adults this might not always be a correct assumption, but as we hypothesize that patients with schizophrenia systematically have a higher variability in the timing of their information processing, a comparison of ERPs that average out these characteristic features not only disguises this phenomenon but distorts the obtained ERPs. As single trial analysis refrains from averaging single EEG intervals, in order to prevent random noise in the data, the recording has to be of high quality if the ERP components have to be successfully identified in raw data for every trial. As raw EEG data show a lot of noise due to artefacts or spontaneous activity which is not event-related, an effective method of filtering is necessary. Wavelet analysis is a new tool that has many possible uses, one being very precise noise filtering (Samar, Bopardikar, Rao, & Swartz, 1999). Multiresolution analysis can be used to decompose the single trial data into different scales or frequency bands (Roth et al., 2007). Thereafter it is possible to choose the frequencies that are essential for the ERP component of interest and analyze the resulting wavelets for selected frequencies only. As delta and theta frequencies play a major role in the generation of the N2 component (S. Karakas, Å. U. Erzengin, & E. Basar, 2000; S. Karakas, O. U. Erzengin, & E. Basar, 2000), the signal can be reduced to these frequency bands in order to facilitate the identification of the N2 peak in the single trials.

Unlike conventional ERPs where data of only one peak per subject is obtained, single trial analysis allows to determine latency and amplitude of every trial of every individual that meets predetermined conditions like a clear maximum or minimum in a defined period of time. Therefore it is possible to calculate the intra-individual variability of the component one is interested in. And of course averaging the obtained single-trial peak data is possible as well, not resulting in a conventional ERP but in an average of all the single-trial maxima or minima. This leads to higher amplitudes as more intra-individual variability of the peak latency is present.

3.3.3 Assessment of spatial distribution

Assessing the source of EEG data measured at the scalp is not easy, as there is generally more than one possible mathematical solution. In the present study we restricted spatial analyses to scalp topography. This allows identification of potential compensatory

mechanisms, but not the localization of the exact brain structure that is responsible for the compensation.

We therefore analyzed the whole frontal electrode row with regard not only to electrode positions that were less negatively activated in patients with schizophrenia but also to ones that showed a higher negativity than in the control group. In order to obtain one individual spatial diffusion variable per person for correlation analysis we calculated the mean difference between the central frontal electrode and two more lateral frontal electrodes, resulting in an individual diffusion index: ((Fz – F7) + (Fz – F8)) / 2. For the position of the frontal electrodes described here see figure 1.

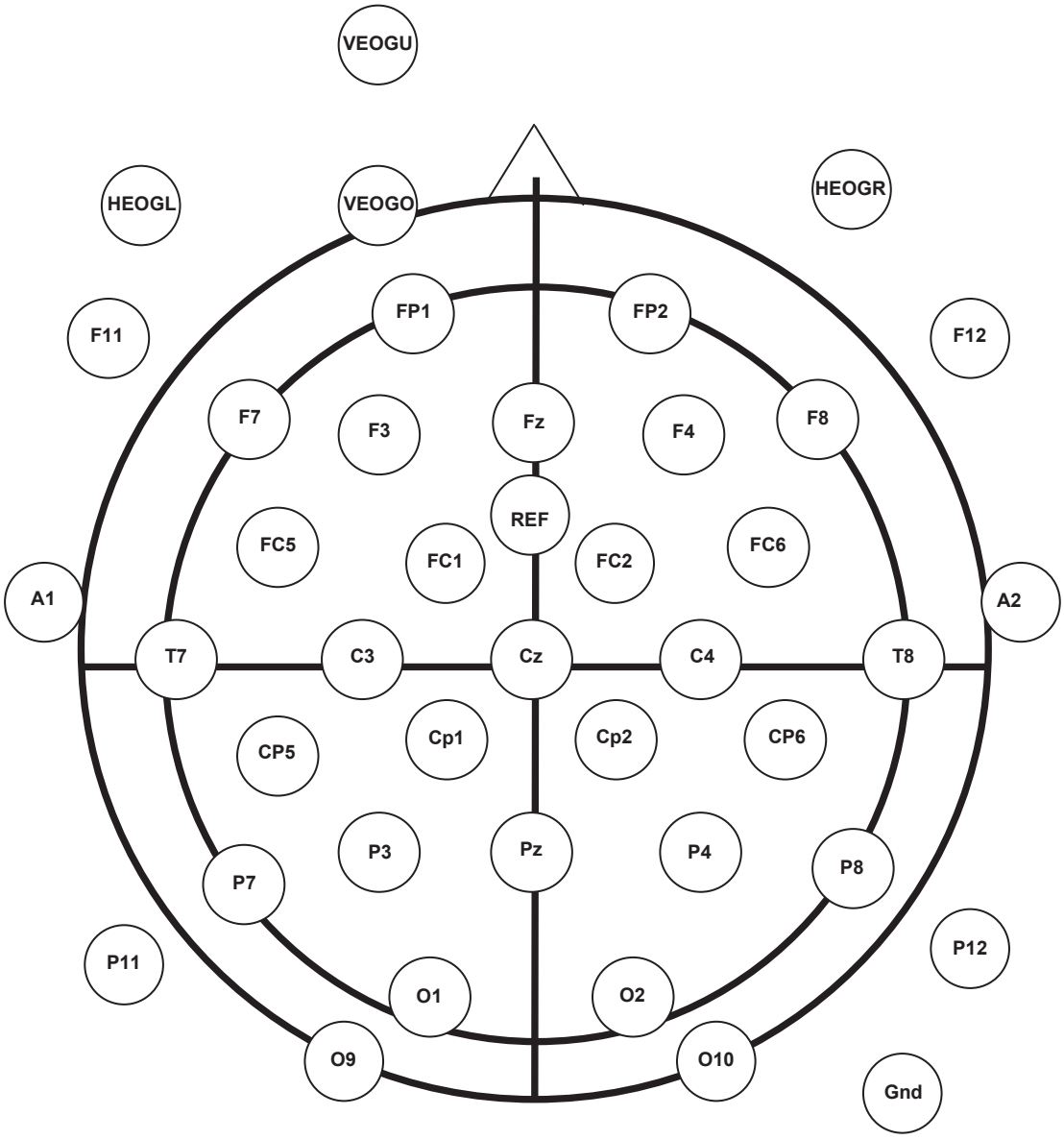

Figure 1: Electrode positions, frontal row used for spatial analysis.

3.4 Assessment of functional capacity (studies I & III)

Ability to work is an essential part of functional capacity and it has important implications for the well-being of a patient as well, like the financial situation, integration in social networks, structured daily routine and self-esteem. Therefore we chose the ability to work as assessment of functional capacity in study I and III.

There are not many suitable German assessments of work ability, especially as we wanted to assess a change in ability over a short time period (three weeks). We decided to apply the Osnabruck Work Capabilities Profile (German: Osnabrücker Arbeitsfähigkeitenprofil, O-AFP), as it has been used for similar purposes before and offers a reliable change index. The O-AFP is an evaluation instrument especially developed for people suffering from mental disorders (Wiedl, Uhlhorn, & Jöns, 2004). The instrument was developed on the basis of the Work Personality Profile (Bolton & Roessler, 1986) with more emphasis on easy application and a wide range of possible applications for various patient groups. Its thirty items are divided into three scales: “Learning Ability”, “Social Communication Ability” and “Adaptation”. The scales were confirmed by factor analyses based on a sample of 194 patients with schizophrenia or schizoaffective disorder (Wiedl et al., 2004). Each item is rated on a five-point rating scale and a detailed description of each level is given for a more objective assessment.

In order to rate the three scales of the O-AFP, it is essential to watch someone carefully during work for some time. As patients took part in a three-week long work therapy where they were assigned certain standard tasks, this was a standardized work setting in which a good evaluation of their working skills was possible. Work capability was evaluated by a specifically trained work therapist responsible for a group of six patients.

3.5 Cognitive training (study III)

3.5.1 General

We designed a single-blind randomised trial comparing planning and problem-solving training with training of basic cognitive functions. Subjects received the training interventions in an inpatient rehabilitation setting during a three-week course of inpatient work therapy.

Patients were shown their respective training tasks in an individual introduction session alone with the trainer in order to be sure that all tasks were completely understood. In all tasks, difficulty was increased adaptively when a preset percentage of answers was correct and within a defined reaction time range. After completion of the training, the trainer discussed the improvement according to the individually achieved level and percentage of errors with the patient and tried to enhance motivation.

3.5.2 Training of basic cognitive abilities

Patients randomly assigned to this training group worked with three different tasks: Processing speed, attention and concentration, and topological memory. In the processing speed task, patients had to react as quickly as possible with the correct key to previously defined visual targets. In the attention and concentration task patients had to compare a picture with three to nine similar pictures shown next to it and to find the one that matched the original completely. In the topological memory task they had to remember three to sixteen pictures of concrete objects or abstract patterns and master a recognition task afterwards. Processing speed and topological memory were trained for 15 minutes each session, attention and concentration was trained twice (between and after the two other tasks) for five minutes.

3.5.3 Training of higher cognitive functions

Patients randomly assigned to the training group focussing on higher cognitive functions used only one training program called “Plan a day”. It consists of a map showing nine different locations and a time schedule for one day with different errands that have to be executed in chronological order. With increasing complexity the number of errands increases, the time necessary for the way between two locations has to be considered but is not always known exactly and not all errands can really be executed because of overlapping time frames. This training program is based on a diagnostic program originally designed for personnel assessment by analysing complex problem solving abilities (Funke & Krüger, 1995). For training purposes it was broken down into basic heuristics like taking priority of errands into account or maximizing the amount of errands executed. Patients in this group used the training program 30 minutes each training session. Despite all simplification it still causes a considerable load on patients’ working memory. Therefore patients were allowed to use paper and pencil to take notes. Besides taking off some of the working memory load this helped patients to plan their moves before executing them instead of solving the exercise by trial and error.

4 SUMMARY OF STUDIES I, II, and III

The three studies all approach the topic of cognitive deficits in schizophrenia from different perspectives. All three are concerned with the idea of linking different levels of research, like working ability as an important part of the functional outcome, schizophrenic symptoms, cognitive ability in standard tests, cognitive variability of reaction times and abnormalities on a more biological level visible in EEG waveforms. The main focus of the three studies was as follows:

Study I: The link between variability of reaction times and working ability (the question of the relation between a hypothesized underlying deficit and functional outcome)

Study II: The link between variability of single-trial N2-waveforms in the EEG and variability of spatial activation during the N2 time-window (the compensation question)

Study III: The link between training of certain cognitive domains and working ability (the question of training potentialities)

For a better overview a brief summary of the studies is given below. The original articles are provided as appendix, all details concerning the three studies are presented there. In the summaries the focus is on the research questions of each of the studies and the main results.

4.1 Study I: "Intra-individual variability in high-functioning patients with schizophrenia" (Rentrop et al., 2010)

Research question

The aim of the first study was to analyse reaction time data in order to find evidence for irregular responses pointing to an underlying deficit in information processing. This was done in a population of high-functioning patients with schizophrenia in order to concentrate on the putative core deficits. In a second step, we explored the relationship between this variable obtained in an artificial test situation to the working ability assessed in work therapy, which is highly relevant for daily life.

Although the higher variability of reaction times in patients with schizophrenia has been known for some time, there are a number of reasons for addressing this parameter in more detail. Against the background of decreased signal-to-noise ratio in local cortical microcircuits it seems promising to investigate variability as a reflection of this underlying neurophysiological disturbance. In order to emphasize the significance of reaction time variability and to analyze whether it can even be regarded as a core deficit, the patients

included in the study were cognitively comparatively well preserved and showed only little abnormalities in common neuropsychological tests, especially in average response times.

Results and discussion

Patients showed almost no cognitive deficits on traditional measures and were therefore labelled as “high-functioning”. Nevertheless their reaction times were significantly more variable than those of matched controls, regardless of the variability measure used (ISD or ICV). This is especially remarkable as the patients’ response times were only slowed in one condition. Therefore in our study the increased variability cannot be explained by patients’ slow responses. An additional analysis made sure that the higher IIV was not only due to fatigue, which would mean that slower responses in the second half of the task would artificially increase variability. In a further analysis it was shown that higher IIV could not be attributed to response strategy, which would mean that the effect of switching between Go and Nogo made the real difference between groups. Although patients showed a small fatigue effect whereas controls showed a small practice effect in the second run, the difference between reaction time variability remained significant when analysing the first run only, where no such effect was present. Task switching did not have a differential effect on the groups at all.

When calculating the parameters of an ex-gaussian distribution – often used to model reaction time distributions – mu and sigma did not differ significantly between groups but tau differed between groups with medium to large effect size. This means that patients showed a higher proportion of very slow responses compared to controls.

Furthermore, their higher IIV in reaction times was linked with poorer performance in working ability. Patients who showed increased variability of reaction times in an experimental Go/Nogo task of approximately 15 minutes also showed poorer working ability as assessed by a blind rater. This emphasizes the potential importance of higher IIV for everyday functioning.

4.2 Study II: “Temporal variability and spatial diffusion of the N2 event-related potential in high-functioning patients with schizophrenia” (Rentrop et al., 2011)

Research question

The aim of the EEG-study was to assess the assumed instability of information processing in patients with schizophrenia on a neurophysiological level. For this purpose we analysed variability of single-trial N2-waveforms measured during a Go/Nogo task in a high-functioning patient group compared to healthy controls. In a second step, we looked at the spatial distribution of activation patterns during the N2 time-window in order to explain the near-to-

normal performance of patients despite their increased N2 single-trial variability. Finally, we analysed the correlation between the temporal and the spatial domain.

Results and discussion

The study analyzed the same patient and control group as study one. The results characterizing our patient sample as “high-functioning” have already been described in the first paper, therefore the second publication focused on the EEG results. In the temporal domain, patients showed increased anterior N2 trial-to-trial variability compared to the control group. The increase in N2 latency variability was observed across conditions and occurred regardless of inhibitory requirements. This emphasizes the fundamental nature of the deficit, as it can be found in the easier condition as well. It therefore disturbs the information processing on an elementary level. However, we did not find a link between electrophysiological variability and behavioural and functional outcome data.

In the spatial domain, patients with schizophrenia showed a more diffuse pattern than healthy controls with less fronto-central activation and additional negative peaks over lateral electrodes, especially in the Nogo condition where more cognitive control was required. This might be the activation of an additional compensatory fronto-temporal network. There was a correlation between temporal N2 variability and spatial diffusion of the fronto-temporal negative activation. It is very interesting that in the Go condition N2 variability did take place but was not accompanied by a significant compensation whereas in the Nogo condition higher temporal variability was correlated with higher spatial diffusion. This could be interpreted as an adaptation to the higher demand of cognitive control in the Nogo condition, where it was necessary to activate compensatory networks in order to maintain a ”near-normal” performance level. In the Go condition spatial compensation obviously did not take place to the same amount although temporal variability of the N2 component was present. It is possible that longer reaction times in the Go condition did not necessarily lead to errors of omission, but only to more variable reaction times and a slightly slowed mean response.

4.3 Study III: “Planning and problem-solving training for patients with schizophrenia: A randomized controlled trial” (Rodewald et al., 2011)

Research question

The effect of cognitive training not only on cognitive deficits but also for functional outcome has already been shown in meta-analyses (McGurk et al., 2007; Wykes et al., 2011). Meanwhile many different training programs have been developed. However, it is still not clear which training is most effective in generalizing to everyday functioning. As cognitive deficits pose a constraint to the functional outcome, the aim of training is not only to improve

the performance on certain tests quite similar to the training task, but to help patients to master their everyday life. Therefore the aim of the third study was to compare two different kinds of training with respect to their effect on working ability. Additionally the performance change in basic and higher cognitive domains (working memory, processing speed, inhibition, planning and problem solving) was analysed according to differential effects associated with the two kinds of training.

All patients worked with a trainings-software from Hasomed, called RehaCom. RehaCom is divided into a variety of subprograms designed for specific remediation of clearly defined neurocognitive deficits. Patients were randomly assigned to one of the two training methods, each took part in a small group with a maximum of five patients. The training groups were lead by one of two psychologists, each lead both kinds of trainings in order to rule out a personal effect on the training outcome. The main outcome variable, the working ability, was estimated by an experienced work therapist, who was blind to the kind of cognitive training patients took part in.

The basic cognition training consisted of a sequence of three different training tasks, which did not require planning or problem solving abilities. The chosen training tasks focusing on basic cognitive functions (processing speed, attention and topological memory) were combined in order to represent a training group practising with a diversified “treatment as usual”. The second group worked with a task taken from the same training software (RehaCom) for a better comparison of influences regarding the user interface and adaptation of training difficulty, but it did not concentrate on basic cognitive functions but on complex problem solving. Therefore the second group was taught to deal with exercises that all belonged to one special task (“plan a day”) of the training software. After each training session the group discussed strategies and implications of the training on everyday life. It was hypothesized that since complex problem solving is associated with some important cognitive deficits found in patients with schizophrenia (like executive functioning) but can be trained with exercises nearer to everyday tasks, therefore enabling strategies to be transferred to real situations more easily, it should have a stronger effect on working ability.

Results and discussion

The hypothesized advantage of the problem solving training group on working ability was not found, as both groups improved alike. The main cognitive variables, measuring planning ability, also improved in both groups, regardless of training. But the plan a day training group improved their performance on the diagnostic Plan-a-day solution time more than the basic cognition training group. As this particular measure is relatively close to the trained task, the originally expected generalization was rather modest. Nevertheless it shows that some differential improvement took place in the group that concentrated on planning ability alone.

There are a number of reasons why the expected differential effect on working ability may not have occurred, like the small time span between pre- and post-test and patients' relatively preserved cognitive ability, which may make it harder to further improve their performance. Furthermore, both groups took part in an effective rehabilitation program, receiving not only the cognitive training but a variety of other therapy elements. The considerable general improvement due to the rehabilitation program may conceal the small differential improvement due to the short specialized cognitive training. And of course it cannot be ruled out that both training tasks have a similar effect on working ability, as different cognitive functions are required in successfully coping with challenges at work, and an effective training of either of them would improve the functional outcome.

5 GENERAL DISCUSSION

Cognitive deficits in people with schizophrenia are in the focus of researchers because they seem to limit the functional outcome of patients after remission (Green, 1996; Kurtz, Wexler, Fujimoto, Shagan, & Seltzer, 2008). As stated in the introduction, research on cognitive deficits related to schizophrenia is essential, amongst others pursuing two goals: Understanding the underlying neurobiological mechanisms of the disorder and developing effective cognitive trainings which are supposed to lead to a persistent positive change in the level of functioning. The three studies presented here pursued both research directions. Studies one and two were concerned with neurobiological mechanisms underlying schizophrenia, the first on a mere behavioural level, the second on an electrophysiological level.

Study one showed that higher intra-individual reaction time variability was present in a high-functioning patient group and even was related to work ability in a naturalistic setting. The increase in short-term fluctuation was found despite a relatively preserved cognitive functioning in other neurocognitive tests. Although variability was increased, mean reaction time was not consistently higher. This is astonishing, given that one consistent result in years of schizophrenia research was that patients have clinically significant cognitive deficits, among other things a clear reduction in speed (Nuechterlein, 1977).

It is evident that not every individual diagnosed with schizophrenia shows a broad cognitive deficit (Palmer et al., 1997). But on the whole the idea to focus on high-functioning patients reflects a new tendency to appreciate the preserved or restored cognitive abilities (Lysaker & Buck, 2008) and enables us to search for patients' effective compensation strategies. Even in times when the label "dementia praecox" is long out-of-date, the picture of the patient determined by more or less unchangeable cognitive deficits still is a very strong feature of the diagnostic category of schizophrenic disorder (Frese, Knight, & Saks, 2009). Showing that despite a neurophysiological deficit patients are able to perform on a near-normal level leads to the question how this can be achieved for other patients as well.

Our data implies that even in inpatient treatment there are groups of patients which show hardly any cognitive deficits compared to matched controls on conventional measures. In conjunction with other recent studies (Palmer et al., 2009) our data contribute to change the deficit-oriented picture of the disorder. We found that our patient sample was able to perform most of our cognitive tests on a normal or near-normal level. That is noteworthy, given the fact that they sought inpatient treatment because of severe problems in their everyday functioning that persisted even though the positive symptoms had subsided.

Only with an analysis of reaction time variability we could show that these high-functioning patients had performance impairments, which were not revealed by analysis of errors or mean reaction time. An irregular response pattern probably not only leads to more

variable reaction times during the quarter of an hour of the Go/Nogo task but has effects on everyday functioning as well. If one cannot perform an easy task reliably and steadily but suffers from disturbances of information processing, this leads to a subjective and objective uncertainty about one's performance capacity. In some cases, it might even cause bystanders to think that patients could perform better if they tried harder, as it can be observed that sometimes for a brief period they can work on a high level. Variability of reaction times and consequently of higher cognitive functions as well could explain why our patient sample – despite their near to normal performance on various neurocognitive variables – still had considerable problems concerning their professional life.

Still, we find that patients' average reaction times are comparable to the ones of control participants and that patients are well able to react as fast as controls. This leads to a reconsideration of the severe slowdown of motoric responses, which was taken for granted since the beginning of experimental schizophrenia research (Keith. H. Nuechterlein, 1977). Part of the slowdown might even be caused by the instability of information processing and the resulting variability of reaction times, as a higher amount of very slow reactions critically influences the mean reaction time.

In spite of normal mean response times we are faced with an instability of patients' reaction times that complicates considerably a good long-term performance. This is important, as it could explain why patients are more exhausted by the same task and have to compensate their instability by other measures like motivation and additional effort. A short break obviously is not sufficient to restore the full cognitive capacity of response speed as patients' reaction times after the break did not profit considerably.

The issue of compensation was analyzed in the second study. The behavioural data implied that to a certain degree compensation must take place, because most performance measures were normal compared to matched controls. But how is this compensation achieved? Although it is still speculative, our EEG results suggest that the compensatory effort leads to the activation of additional lateral frontal networks. That fits the results of fMRI studies, concluding that for patients with schizophrenia additional networks seem necessary for compensation in order to result in a normal behavioural performance (Kim et al., 2010). It remains an open question for how long the patients manage to sustain the activation of this additional network. But from behavioural observation it can be assumed that this additional activation goes along with increasing fatigue, as it could be observed that most patients were rather exhausted after the Go/Nogo task. Furthermore, the behaviour data revealed a significant interaction with group for the two different runs in the Infrequent Go task, with patients performing more slowly and more variably in the second half of the Go/Nogo task compared to controls. This could be interpreted as a first sign of fatigue in the part of the task

that did not require a continuous motor response and therefore seemingly allowed saving some effort.

The second study showed that temporal variability could also be found in electrophysiological components. Furthermore, it seems to be a very fundamental feature, as it occurred in both conditions, Go and Nogo. Nevertheless, in the Nogo condition, where inhibition is required and the demands on cognitive control rise, the additional activation was linked to the temporal variability. Therefore the difficulty of the task could actually have an effect on compensation.

But did we find a cognitive or neurophysiological impairment that can claim to be a core deficit? As was explained earlier, the idea of a core deficit is to account for numerable clinical features of the illness with one underlying dysfunction. The hypothesis of disconnected microcircuits in the frontal lobe would offer a theoretical background for a core deficit that could explain various deficits (Rolls et al., 2008). However, we did not show a direct connection between microcircuits of the brain, higher IIV in single trials and increased IIV in reaction times. Therefore it is not possible at this point in time to call higher IIV a core deficit. Furthermore, it can be debated whether increased IIV would be the core deficit as such or just a measure more directly linked to a more fundamental neurophysiological disturbance. Finally it has to be mentioned that not every patient showed a higher IIV. That would make additional explanations (like subgroups, medication, or extremely high premorbid functioning) necessary in order to explain why a core deficit is not present in every patient.

In summary, IIV may be one more promising candidate for the underlying core deficit or, rather, a promising candidate for a cognitive measure of the underlying neurobiological deficit. Especially its relation to working ability and therefore its meaning in everyday life is impressive and emphasizes the results of Wexler's study (Wexler & Nicholls, 2004). But it is still not clear how increased IIV is caused exactly, although Winterer's hypothesis of increased noise in fronto-cortical networks (Winterer et al., 2006) seems plausible.

Another flaw in the theory is that there is no positive correlation between IIV on electrophysiological and IIV on behavioural level. It can be argued that effective compensation mechanisms might conceal such a relation. But simultaneously this argumentation reduces the importance of IIV on an electrophysiological level, as compensation would be so effective that N2 IIV seems to have no effect on behavioural measures and therefore is unlikely to be the searched for core deficit that leads to everyday impairments. Another point to be noted is that since the N2 is a typical Nogo-component but reaction times can only be assessed in a Go-component the correlation does not really make sense, as N2-IIV and reaction time IIV measure different things. Of course there is an N2 in the Go condition and we assessed its single-trial IIV as well, but it does not have such an importance for the correct reaction as it has in Nogo. To correlate both IIVs, another

paradigm should be used, for instance a task where the inhibition of the prepotent motor response is followed by an action that leads to a measurable reaction time like the press of a second button. This would add task switching to mere inhibition but then it would make more sense to correlate a Nogo-related ERP component and a Nogo-related reaction time IIV. A third explanation could be that N2 is not the only component that is involved in the motor response and that could be affected by increased IIV. Maybe the higher cortical noise affects other parts of the information processing as well or even more, leading to different sources of variability and therefore concealing a direct link between N2 variability and reaction time variability. Possibly expecting N2 variability to correlate with reaction time variability just means too much of a simplification given the complex interaction of different brain regions during the interpretation of visual information, the reaction preparation and execution. It has also been proposed that in schizophrenia not only the frontal microcircuits are disturbed but also the macrocircuits connecting different brain regions, especially the cortico-cerebellar-thalamo-cortical circuit (Andreasen et al., 1999). This cognitive dysmetria hypothesis would explain why one single ERP component is not enough to detect substantial common variance with reaction times. Finally, it has been stated that intraindividual variability is not a uniform concept but has different effects on the neurophysiological and the behavioural level (Fjell, Rosquist, & Walhovd, 2009).

In the first two studies we were concerned with the understanding of the underlying neurobiological mechanisms. In the third study we concentrated on implications of this research area for possible cognitive trainings in order to improve the functional outcome. Noting the already achieved normal performance of patients in average reaction times is one thing, helping patients to increase the amount of unimpaired test results – especially in higher cognitive functioning – is another. To achieve this we took a clinical approach using results of basic research trying to improve patients' cognitive abilities, especially in situations that resemble the complexity of real life. Effective compensation must have taken place for our high-functioning patient group in the easier tasks, but tests designed for planning and problem solving showed patients' deficits in this highly relevant area. Therefore higher cognitive functioning sample seemed a good candidate for a new cognitive training program.

Knowing that functional outcome is limited by cognitive performance does not necessarily mean that training of cognitive performance first improves cognitive abilities and then automatically leads to a better functional outcome. Likewise it is speculative whether normalizing patients' IIV leads to better cognitive functioning and a better performance at work or other everyday tasks. The positive results of the cognitive training study are that these high functioning patients significantly improved firstly their planning ability as well as other basic cognitive performances and secondly their work ability within a period of time approximately lasting a month. Given the pressure to offer cost-effective treatments and to

treat inpatients as briefly as possible, this result gives hope that the inpatient setting is able to change the patients' performance considerably. But it is not possible to attribute the better work ability to the cognitive training alone as – for ethical reasons – no control group without any cognitive training was included in the study and the cognitive training was only one component of a rich therapeutic setting.

The training study shows that a generalization effect to cognitive tests not clearly linked to the training is difficult in this time-frame and needs either more time or more attention to transfer during training. Generalization did not take place in other training studies as well (Benedict, Harris, Markow, & McCormick, 1994; Dickinson et al., 2010). In one study comparable to ours in using RehaCom software and similar training modules like our control group for 14 sessions, the cognitive performance after the training improved significantly in most trained neuropsychological domains but did also not generalize to functional outcome (d'Amato et al., 2011). Therefore transfer to everyday functioning cannot be assumed to happen automatically but has to be an explicit part of the training program as well. Even though this was attempted in the planning training group, it is obviously necessary to bestow even greater care on it.

Finally it should be kept in mind that cognitive training is but one component in the broad rehabilitation program necessary for patients' optimal benefit. It seems that at first (Green et al., 2000), the importance of neurocognition was overestimated, as other predictors were not taken into account. Meanwhile, social cognition seems to be another very important component in addition to other cognitive abilities (Bora, Eryavuz, Kayahan, Sungu, & Veznedaroglu, 2006). Recent studies suggest that cognition only explains 20% of the variance of functional outcome (Brekke, Kay, Lee, & Green, 2005; Fett et al., 2011), therefore it seems not surprising that a differential effect on working ability after a short training could not be found. Neurocognition seems to have its effect on functional outcome especially through other mediator variables (Brekke et al., 2005), by enhancing the prerequisites necessary for social abilities. But as transfer even in the cognitive domain remains scarce, the generalisation to social cognition remains speculative and should be guaranteed by special social trainings. Therefore our primary outcome may have been too "far" for the small additional effect the specialized training had on cognition, let alone working ability.

Bell and colleagues (Bell et al., 2009) even claim that perceived social discomfort additionally mediates the process, and despite a better statistical fit their model including neurocognition, social cognition and perceived social discomfort only explained less than 20% of variance regarding the rehabilitation outcome. That may be an explanation for our problem in finding a differential effect in working ability. Even though we concentrated on the more cognitive aspect of working ability (the subscale "learning ability") it may be argued that

learning takes place in a social environment and is influenced by social aspects like being able to listen while being observed by others, being able to signal lack of understanding, being able to broach a subject again in a case of uncertainty, or being able to notice praise or reproach. Therefore it may be not sufficient even for a predominantly cognitive training to concentrate on cognitive problem solving abilities alone without including social problem solving abilities as well.

Possibly the computer training should be combined with a more practical approach in the patients' environment. Certainly the CAT (cognitive adaptation training) is the approach least similar to our predominantly computer assisted training, as it does not work with abstract cognitive training at all and focuses on patients with a very poor cognitive performance. Most importantly the focus is not on restitution of cognitive deficits, but on the use of remaining abilities to compensate for the existing deficits. A combination of computer assisted training with a CAT type compensatory training could prove valuable. The CAT would not be optimal for inpatient treatment, but it could set an example in accordance with its individually adaptive procedure according to the previously assessed cognitive impairment. There are 6 CAT classifications for which interventions can be targeted: Apathy/ poor executive function, apathy/ fair executive function; disinhibited/ poor executive function, disinhibited/ fair executive function; mixed/ poor executive function; mixed/ fair executive function (Velligan et al., 2008). A more practical approach as well as more individual contact as well as a more differentiated intervention strategy on the basis of the assessed deficits could prove beneficial. Surely the CAT is an extreme example for a different treatment approach, but it shows alternative options compared to our procedure.

Besides research focussing on the additional benefit of adding more social and transfer components to a cognitive training, the question of duration of training necessary to have a lasting effect on cognitive abilities remains unanswered. Short-time interventions like ours have some effect, but seemingly the nine training sessions were not enough to cause a differential benefit on the chosen cognitive domains. It would be very interesting to examine whether a longer training could result in differential effects. And further studies should address the amount of training necessary after the completion of the computer training in order to maintain the improved cognitive abilities. Are booster sessions at regular intervals after short trainings necessary to keep performance on the higher level? Are there special conditions that magnify or reduce the normal training effect, like medication, training frequency, background of the trainer or rewards for patients' improvements? Is it more effective to concentrate on one cognitive function at a time or to compose a training that covers diverse cognitive components and therefore has a broad training aim?

The three studies tried to link different levels of cognitive processes. Accordingly the question arises, on which level a cognitive training should focus preferentially. Lately a so-

called “neuroplasticity-based training” working on a basic level of information processing – early auditory processing and working memory operations – has proven rather successful (Fisher, Holland, Subramaniam, & Vinogradov, 2010). The idea it follows is to generate reliable and stable neurological responses to incoming information. For verbal speech that means neuronal responses precisely representing the frequency, the timing, and the complex sequential relationships between different sounds. This indirectly aims at reducing temporal variability in information processing, as a high number of trials is used in the training and complexity is very low at first. This is a bottom-up process, trying to restore or develop basic abilities that are needed for complex tasks like following and joining a verbal discussion in a group. Other trainings like our problem-solving training worked with higher cognitive functions and concentrated on heuristics to break complex problems down to simpler and more easily solvable problems, therefore rather following a top-down approach. These kinds of trainings do not hope to fully restore basic abilities but rather attempt to help patients find ways to compensate for some of their deficits. This seems to be a rather promising way as well, according to a recent meta-analysis that emphasized the effectivity of strategic trainings combined with additional rehabilitation programs (Wykes et al., 2011). But maybe a combination of both approaches, or - in other words - a training designed to improve abilities on different levels could prove particularly successful, at least in patients with broad deficits.

Finally the question arises whether a training could be designed that specifically aims at reducing temporal variability in information processing, regardless of modality or task. Could it rely on response times alone or would it need electrophysiological measures as biofeedback? Would it work to change information processing stability by reward, or would it need some kind of medication to optimize the frontal signal to noise ratio? And would it help in stabilizing information processing in daily life, or would it only work during the training? These questions are not easily answered and require thorough research, at best directly comparing different approaches in order to find the most effective alternative.

Altogether, the three studies presented tried to focus on associations between different levels of cognition in schizophrenia. One study linked IIV of response times to work ability assessed in work therapy, another one linked temporal variability on electrophysiological level with additional spatial activation in a task that required inhibition and the third one showed that even a very short intervention with a computer-assisted new training task improved cognition and work ability. All studies raise a number of questions to be addressed in future research. Importantly the core deficit question should be pursued further in order to get a solid theoretical foundation for the development of cognitive training programs.

6 ABSTRACT

Research on cognition in people with schizophrenia has provoked a lot of interest for two reasons: It offers a better understanding of the neurobiological components of the disorder and it helps creating effective treatments for cognitive deficits, which limit the possible functional outcome after remission. The three studies presented here are all concerned with cognitive deficits in schizophrenia, but they focus on different levels, from electrophysiology to work ability in a clinical setting. The first two studies addressed the question of an underlying core deficit of the disorder, which might lead to the clinical features of the illness, in particular the commonly observed broad cognitive impairments. In both studies we hypothesized that increased intra-individual variability could be found in a high-functioning sample of patients with schizophrenia. The first study concentrated on response times whereas the second used an electrophysiological measure. The third study directly compared two cognitive trainings which work on different levels – one working with basic cognitive functions like memory and attention and one specifically training planning and problem solving as a part of higher cognitive functioning. The first study did not only find increased intra-individual variability in high-functioning patients with schizophrenia but could show an association between increased variability of response times and poorer work ability. The second study found that on an electrophysiological level increased temporal variability was found when analysing single trials of the N2 component, and that higher variability was linked with a more widespread activation during the N2 time-window. The third study comparing the two trainings did not find a clear advantage of one over the other. Both trainings lead to some improvements in cognitive functioning and work ability. There was an indication that planning ability improved more when trained directly instead of being trained via basic cognitive abilities. The first two studies emphasize the importance of intra-individual variability for schizophrenia and its occurrence on different levels. The association between response variability and work ability further highlights the importance of this measure. The third study indicates that a new training focussing specifically on planning and problem solving had an effect comparable to that of a more conventional training for patients with schizophrenia. Its results show how important it is to directly compare different kinds of training with each other and with a control group. In conjunction, the three studies provide the basis for further research into putative cognitive and neurophysiological core deficits of schizophrenia, which could provide a theoretical basis for the development of cognitive training programs.

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8 APPENDICES

8.1 CURRICULUM VITAE

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Voluntary Service:

1998 – 1999 Gap year (Freiwilliges Soziales Jahr)

Academic Career:

1999 – 2005 Study of Psychology at the Ruprecht-Karls-University Heidelberg

2005 Diploma in Psychology (Dipl.-Psych.)

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Since 2007 PhD studies at the Ruprecht-Karls-University Heidelberg

Publications

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Rodewald, K., Rentrop, M., Holt, D.V., Roesch-Ely, D., Backenstraß, M., Funke, J., Weisbrod, M., Kaiser, S. (2011). Planning and problem-solving training for patients with schizophrenia: A randomized controlled trial. *BMC Psychiatry* 11:73.

Rentrop, M., Roth, A., Rodewald, K., Simon, J., Metzler, S., Walther, S., Weisbrod, M., Kaiser, S. (2011). Temporal variability and spatial diffusion of the N2 event-related potential in high-functioning patients with schizophrenia. *Schizophrenia Research* 131(1-3): 206-213.

8.2 DECLARATION

Erklärung gemäß § 8 Abs. 1 Buchst. b) der Promotionsordnung der Universität Heidelberg für die Fakultät für Verhaltens- und Empirische Kulturwissenschaften

Ich erkläre, dass ich die vorgelegte Dissertation selbstständig angefertigt, nur die angegebenen Hilfsmittel benutzt und die Zitate gekennzeichnet habe.

Erklärung gemäß § 8 Abs. 1 Buchst. c) der Promotionsordnung der Universität Heidelberg für die Fakultät für Verhaltens- und Empirische Kulturwissenschaften

Ich erkläre, dass ich die vorgelegte Dissertation in dieser oder einer anderen Form nicht anderweitig als Prüfungsarbeit verwendet oder einer anderen Fakultät als Dissertation vorgelegt habe.

Name, Vorname_____

Datum, Unterschrift_____

8.3 ORIGINAL ARTICLES

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Intra-individual variability in high-functioning patients with schizophrenia

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ABSTRACT

Intra-individual variability of reaction times (IIV) can be employed as a measure of the stability of information processing, which has been proposed to be fundamentally disturbed in schizophrenia. However, the theoretical and clinical significance of IIV is not clear, in part because it has previously been investigated in subject groups with generalized cognitive impairment. Therefore, the purpose of the study was to assess IIV in high-functioning patients with schizophrenia and relatively preserved cognitive performance. 28 high-functioning patients with schizophrenia and 28 controls performed a Go/Nogo task and a Continuous Performance Test. In contrast to average measures of task performance, IIV differentiated consistently and with large effect size between groups. Modelling with an Ex-Gaussian distribution revealed that patients have a higher proportion of slow responses reflected by an increased tau parameter. The tau parameter was correlated with work capability in the sample with schizophrenia. In conclusion, IIV is an easily obtained measure, which is highly sensitive to fundamental cognitive deficits not directly visible in a high-functioning patient group. The response pattern with more exceedingly slow reactions could reflect a core deficit in the stability of information processing. The relationship with work capability suggests investigation of IIV as a clinical measure.

1. Introduction

Patients with schizophrenia show a broad range of cognitive impairments, which are generally assessed with average measures of task performance. Another approach is to measure intra-individual variability (IIV) reflecting short-term fluctuations in task performance (Stuss et al., 2003; Klein et al., 2006). Here, variability is not regarded as uninformative 'noise', but as a source of information on the stability of cognitive processing. An increase in intra-individual variability has been established in patients with schizophrenia, which regards mainly reaction time variability but also variability on time estimation tasks (Nuechterlein, 1977; Schwartz et al., 1991; Vinogradov et al., 1998; Matthysse et al., 1999; Kaiser et al., 2008; Carroll et al., 2009). However, its functional and clinical significance has received little attention in comparison with the vast literature on impairment of aggregate measures of task performance. In our view recent developments require a new look at IIV in schizophrenia.

First, influential models on the neurophysiological basis of schizophrenia emphasize an instability of information processing in the brain. Andreasen et al. (1998) have developed the cognitive dysmetria concept, which postulates a fundamental dysfunction in the synchronization of both thought and action caused by a disconnection of fronto-thalamic-cerebellar circuits. More recently, Winterer and others have suggested an increase in noise in frontal cortical networks in schizophrenia, which has been supported by electrophysiological and functional imaging data (Winterer and Weinberger, 2004; Winterer et al., 2006). Both approaches postulate an instability of information processing on a neurophysiological level, which also leads to an impairment on cognitive tasks of attention and executive function. While the latter impairment can be observed on aggregate measures of task performance, measurement of IIV might be more sensitive for the underlying instability of information processing. However, identification of such specific behavioural markers for instability is severely hindered by the broad cognitive impairments usually observed in patients with schizophrenia (Heinrichs and Zakzanis, 1998). Increased IIV is usually only one of the abnormalities along with increased error rates and slower reaction times. In order to reduce unspecific effects of broad impairment, recent studies have started to focus on cognitively advantaged patients (Heinrichs et al., 2008). In other words, if increased IIV truly reflects a schizophrenic core deficit in stability of information processing, it should be found in high-functioning patients with schizophrenia with relatively preserved cognitive function.

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Second, recent research on IIV has employed sophisticated models to appropriately describe reaction time distributions. This is of high interest, because different aspects of these distributions could reflect specific underlying disturbances (Vinogradov et al., 1998). There is some evidence that the increase in variability is mainly caused by a positively skewed distribution with a higher proportion of long reaction times (Belin and Rubin, 1995; Birkett et al., 2007). In ADHD the modelling of reaction times as an Ex-Gaussian distribution to reaction time data has proven to be useful (Leth-Steensen et al., 2000), but has not been applied to schizophrenia. The Ex-Gaussian distributional model provides quantitative measures of the distributional properties of reaction times for each individual (Heathcote, 1996; Luce, 1986). This approach assumes that the response time distribution can be modelled as the convolution of a normal distribution and an exponential distribution. The model is defined by three parameters: μ (mu), the mean of the normal component, σ (sigma), the standard deviation of the normal component, and τ (tau), the slope of the exponential component. Tau as mean of the exponential part of the distribution therefore provides a measure for asymmetry or skewness: A larger tau corresponds to an increase in the tail of the probability density function.

Third, it has been suggested that consistency of performance as measured by IIV might be related to real-world functioning (Stuss et al., 2003). In an important pilot study Wexler and Nicholls (2004) could show a relation to work outcomes in schizophrenia. However, their study combined a variety of tasks and their measure of variation combined short-term (seconds) and long-term variation (days). Therefore, their findings suggest a role for IIV as a direct measure of cognitive consistency in a working context, but a specific relationship with short-term fluctuations of performance remains to be established.

Therefore, the aim of the study was to assess and model IIV of reaction times in a group of high-functioning patients with schizophrenia. For this purpose we used a Go/Nogo task and a Continuous Performance Test (CPT). The study addressed three related research questions:

(1) Do patients with schizophrenia and relatively preserved cognitive test performance show increased IIV of reaction times?
(2) Does fitting of an Ex-Gaussian distribution allow for a quantitative description of the pattern of increased IIV in patients with schizophrenia?
(3) Is increased IIV related to working ability in high-functioning patients with schizophrenia?

2. Methods

2.1. Subjects

We recruited 28 inpatients satisfying DSM-IV criteria for schizophrenia or schizoaffective disorder confirmed by diagnostic interview (M.I.N.I.; Sheehan et al., 1998). We excluded any patient with another Axis I disorder, substance abuse in the last 2 months or neurological problems. Patients were admitted to participate in the preparation for a demanding rehabilitation program including professional training. Therefore, this group was expected to represent a high-functioning population. All patients gave written informed consent and the study was carried out in accordance with the Declaration of Helsinki. All patients were medicated with atypical antipsychotics, two additionally took typical antipsychotics. Five patients were treated with antidepressant medication and one with a mood stabilizer. Diagnostic interviews and psychopathological assessment were conducted in a separate session. Neuropsychological data were collected in two sessions to keep up the patients' motivation and attention. Overall, the assessments took about 3 h.

We further recruited 28 healthy controls from hospital staff matched for gender, age and years of education (see Table 1). They were screened with the M.I.N.I. for Axis I disorders, which were exclusion criteria. Control subjects received 30 euros for participation.

2.2. Measures

2.2.1. Working memory and estimated premorbid intelligence

The MWT is a German multiple choice vocabulary test to estimate premorbid intelligence (Lehrl et al., 1995). The following subtests from the WAIS III (Wechsler, 1997) were used to assess verbal working memory maintenance and manipulation: digit forward, digit backward and letter–number sequencing. The Corsi Block-Tapping Task was used to assess spatial working memory maintenance and manipulation analogous to digit span forward and backward (Milner, 1971).

Table 1
Demographic characteristics, psychopathologic assessment, estimated premorbid intelligence and working memory test raw scores for the patient and control groups.

	Healthy controls	Patients with schizophrenia	*t*-value	Degrees of freedom	*P*
Age	25.50 (9.40)	26.07 (6.90)	−0.26	54	0.80
Years of education	14.40 (2.60)	14.32 (2.70)	0.03	54	0.98
Male/female	20/8	20/8			
PANSS positive		12.79 (2.96)			
PANSS negative		18.43 (4.69)			
PANSS global		32.50 (5.67)			
MWT-B raw score	27.21 (5.20)	27.86 (4.17)	−0.51	54	0.61
MWT-B estimated IQ	103.25 (12.18)	103.61 (10.20)	−0.11	54	0.91
Digit span forward	9.46 (1.91)	9.30 (2.11)	0.31	54	0.76
Digit span backward	7.00 (2.14)	6.33 (2.20)	1.14	54	0.26
Letter number sequencing	11.36 (2.83)	10.67 (2.54)	0.95	54	0.35
Corsi forward	8.93 (1.65)	8.81 (1.77)	0.25	54	0.81
Corsi backward	8.86 (2.07)	8.07 (1.64)	1.55	54	0.13

2.2.2. Go/Nogo task

In an uncued Go/Nogo task subjects were required to answer as fast and correctly as possible by pressing the left mouse button to a visual target stimulus. To a second non-target visual stimulus, no reaction was required. In the Infrequent-Go condition the stimulus requiring response occurred in 20% of trials. In the Frequent-Go condition the stimulus requiring response occurred in 80% of trials and this prepotent response had to be inhibited in the remaining 20% of trials. In one trial the stimulus was presented for 120 ms followed by a fixation cross for 1340 ms. The sequence of trials within each block was pseudorandomized and no more than two rare events occurred in direct sequence. In each of the two runs, we used a mixed sequence of 4 Infrequent-Go and 4 Frequent-Go blocks of 40 trials, separated by a short break so that participants could rest. Each run had a duration of 8 min and 26 s. Overall, the completion of the Go/Nogo task took about 20 min.

2.2.3. Continuous Performance Test (CPT)

In this study we used the modified CPT-OX developed by Cohen and Servan-Schreiber (1993) and Fallgatter et al. (1997), including Go and Nogo trials. It consists of 400 letters on a computer monitor presented in pseudo-random order, the twelve letters A–H, J, L, O and X each shown for 150 ms at 1650 ms intervals. Participants were instructed to respond as quickly as possible each time the letter 'O' was followed directly by letter 'X' (Go condition). The other 10 letters (A–H, J and L) required response inhibition if they immediately followed the letter O (Nogo condition) and served as meaningless distractors when presented subsequent to any other letter than O. A session lasted about 14 min and consisted of 114 presentations of the letter O with 57 Go trials followed by an X and 57 Nogo trials followed by another letter except O or X.

2.2.4. Assessment of work performance: The Osnabruck Work Capabilities Profile

The Osnabruck Work Capabilities Profile (German: Osnabrücker Arbeitsfähigkeitenprofil, O-AFP) is an evaluation instrument used to assess the work capability of people suffering from mental disorders (Wiedl et al., 2004). The instrument was developed on the basis of the Work Personality Profile (Bolton and Roessler, 1986) with more emphasis on easy application and a wide range of possible applications for various patient groups. Work capability was evaluated by a specifically trained work therapist responsible for a group of six patients receiving three weeks of work therapy, which is the standard initial phase in the treatment program.

2.3. Data analysis

Overall correctness of task performance was calculated for Infrequent-Go and Frequent-Go conditions as well as the CPT by calculating the sensitivity index d' (Green and Swets, 1966). IIV was assessed by intra-individual standard deviation (ISD) of reaction times. Since ISD can be numerically higher in individuals with longer reaction times, it has been suggested to additionally employ the intra-individual coefficient of variance (ICV), which is calculated by dividing ISD by the individual mean reaction time (Wagenmakers and Brown, 2007).

For the computation of the Ex-Gaussian distribution we used the RTSYS-software applied by Heathcote (1996). The fit of the estimation depends on the number of trials available, it is proposed to use more than 100 data points per individual and condition (Heathcote et al., 1991). Since there were maximally 32 correct trials per run in the Infrequent-Go condition and maximally 57 correct trials in the CPT, we performed this

analysis exclusively for the Frequent-Go condition, where more than 100 trials were available per run. Only correct reaction times were used in the estimation of these measures, reaction times smaller than 100 ms or higher than 3 individual standard deviations above the individual mean were discarded.

t-tests between groups were performed with significance level set to $P<0.05$. For the analyses involving within-subject factors we performed mixed ANOVAs with group as between-subject factor and the respective within-subject factors. For correlations between IIV and work capacity (OAF-P total score) as well as illness duration we calculated Pearson's *r* with each of the Ex-Gaussian distribution parameters. For calculations we used Statistica Version 8.0 (StatSoft, Inc., 2007).

3. Results

3.1. Premorbid intelligence and working memory

Groups did not differ significantly on estimated premorbid verbal intelligence (MWT-B) and working memory test scores (see Table 1).

3.2. Errors and mean reaction time (Go/Nogo and CPT)

In the Infrequent-Go condition of the Go/Nogo task the signal detection measure d' was significantly lower in the patient group, which indicates impaired accuracy of task performance (see Table 2). The effect size was medium with $d=-0.53$. In the Frequent-Go condition and the CPT, d' did not show a significant difference between patients and controls.

Errors of omission and errors of commission did not differ significantly between groups in the Go/Nogo task. In the CPT patients had a higher percentage of errors of omission.

The reaction time differences between groups did not reach significance in any task.

3.3. Reaction time variability (Go/Nogo and CPT)

The difference between the two groups' ISD in the Frequent-Go condition was highly significant with a large effect size of $d=1.02$ (see Table 2). ISDs between the two groups also differed significantly in the Infrequent-Go condition (effect size $d=0.86$) and the CPT (effect size $d=0.81$). When calculating the ICV, differences between groups remained significant for all task conditions.

3.4. Effects of time on task (Go/Nogo and CPT)

To rule out differential effects of practice or fatigue on IIV, we analysed the course of reaction times and ISD for both groups. Since this analysis aimed at differential effects between groups, we report only interactions involving the factor group.

For the Go/Nogo task, we divided the two runs in two equal halves. We then performed a repeated measures ANOVA with group (controls and patients), run (first and second) and half (first and second half of the respective run) with mean and ISD of reaction time as dependent variables. There was no interaction involving the factor half in both tasks. In the Infrequent-Go task there was an interaction between group and run for mean reaction time ($F(1, 54)=8.02$, $P=0.006$) and ISD ($F(1, 54)=4{,}23$, $P=0.04$). While control subjects tended to respond faster and less variable in the second run, patients showed the opposite pattern. However, it has to be emphasized that the ISD differences between groups were still significant, when analysing the first run only ($t(54)=-2{,}11$; $P=0.04$). In the Frequent-Go task there was no interaction involving group.

For the CPT, we divided the tasks in three time blocks. We then performed a 2 (group) × 3 (time) ANOVA with mean reaction time and ISD as dependent variables. There was no significant interaction.

3.5. Effects of switch cost (Frequent-Go)

Another possible explanation for the higher IIV in patients might be their inability to flexibly switch between targets and non-targets. In other words an increased switch cost might lead to higher IIV. To rule out this alternative explanation we calculated reaction times and IIV for switch and non-switch trials separately. Only the Frequent-Go condition provided a sufficient number of both trial types for appropriate estimation. For this condition we performed 2 (group) × 2 (trial type) repeated measures ANOVAs with mean reaction time and ISD as dependent variables. There was no significant interaction on any of these two measures.

3.6. Ex-Gaussian modelling of reaction time distribution (Frequent-Go)

For every participant Ex-Gaussian parameters were estimated for all correct responses in the Frequent-Go condition (see Table 3 and Fig. 1), only 1.45% (patients) and 1.18% (control) of the responses were excluded as outliers. Chi-square tests indicated that the estimated Ex-Gaussian distribution did not differ significantly from the observed reaction time data in any case indicating appropriate fit (all $P>0.1$). Mu and sigma did not differ significantly between groups. Tau differed between groups with medium to large effect size ($d=0.78$).

In an exploratory analysis we investigated the relationship between the Ex-Gaussian and clinical parameters. We assumed that

Table 2
Mean reaction time, intra-individual standard deviation of reaction times (ISD), intra-individual coefficients of variation (ICV) and accuracy of task performance (measured by the sensitivity index d' and errors); standard deviations in brackets. *P*-values <0.05 in bold font.

		Healthy controls	Patients with schizophrenia	*t*-value	Degrees of freedom	*P*
Infrequent-Go	Mean RT (s)	426.79 (46.98)	459.39 (73.31)	−1.98	54	0.053
	ISD (s)	115.15 (23.95)	146.73 (46.16)	−3.21	54	**0.002**
	ICV	0.27 (0.05)	0.32 (0.08)	−2.53	54	**0.014**
	d'	4.85 (0.33)	4.63 (0.49)	2.02	54	**0.048**
	Errors of omission (%)	0.50 (1.54)	1.90 (4.89)	−1.44	32.27	0.16
	Errors of commission (%)	0.45 (0.46)	0.73 (0.77)	−1.64	44.02	0.11
Frequent-Go	Mean RT (s)	341.09 (45.11)	362.80 (63.09)	−1.48	54	0.14
	ISD (s)	83.72 (19.19)	112.34 (35.3)	−3.74	54	**0.0005**
	ICV	0.25 (0.05)	0.31 (0.08)	−3.28	54	**0.002**
	d'	3.75 (0.73)	3.42 (0.83)	1.56	54	0.12
	Errors of omission (%)	1.00 (1.39)	1.62 (3.05)	−0.97	54	0.34
	Errors of commission (%)	12.89 (10.49)	17.52 (11.94)	−1.54	54	0.13
CPT	Mean RT	453.53 (110.82)	496.27 (115.01)	−1.39	52	0.17
	ISD	86.42 (42.91)	130.50 (62.84)	−3.01	52	**0.004**
	ICV	0.18 (0.07)	0.26 (0.09)	−3.41	52	**0.001**
	d'	4.41 (0.59)	4.04 (0.83)	1.91	52	0.06
	Errors of omission (%)	1.26 (1.87)	4.37 (5.79)	−2.66	52	**0.01**
	Errors of commission (%)	0.78 (2.68)	0.51 (1.01)	0.47	52	0.64

Table 3
Analysis of estimated Ex-Gaussian reaction time parameters mu, sigma and tau. These parameters represent the mean and the standard deviation of the normal part of the Ex-Gaussian function and the slope of the exponential part of the distribution. Standard deviations are given in brackets. *P*-values <0.05 in bold font.

Frequent-Go	Healthy controls	Patients with schizophrenia	*t*	*df*	*P*
Mu	270.34 (50.57)	268.61 (56.62)	0.12	54	0.90
Sigma	31.81 (14.85)	38.61 (21.18)	−1.39	54	0.17
Tau	67.01 (20.91)	87.37 (30.42)	−2.92	54	**0.005**

a marker for the illness should be present across different illness durations and symptom expressions. First, we performed correlations with duration of illness. There was no significant correlation with sigma or tau. However, we found a significant correlation between mu and illness duration ($r=0.42$, $P=0.03$) for 27 patients after elimination of one outlier after visual inspection of the scatterplot. Second, we computed correlations with PANSS positive and negative subscales. There were no significant correlations between any of the Ex-Gaussian parameters and symptoms (all $P>0.1$).

3.7. Correlations within the schizophrenia group with a measure of work capability

The correlation between the estimated tau parameter and the O-AFP global score was $r=-0.60$ ($P=0.001$) for the 26 patients with O-AFP scores available (see Fig. 2). Neither the correlation with mu ($r=-0.25$) nor with sigma ($r=-0.21$) reached significance (all $P>0.2$).

We also addressed the relationship between work capability and ISD, which is more commonly employed than the parameters of the Ex-Gaussian distribution and can be extracted from all three task conditions (Frequent-Go, Infrequent-Go, CPT). The results revealed significant negative correlations for the Frequent-Go ($r=-0.53$, $P=0.006$) and the Infrequent-Go conditions ($r=-0.45$, $P=0.02$), but the negative correlation for the CPT reached trend level only ($r=-0.36$, $P=0.07$).

4. Discussion

The present study yielded the following main findings: First, IIV showed significant differences at the group level between patients with schizophrenia and a matched control group even though other measures of cognitive functioning were similar. Second, increased IIV of the group with schizophrenia was due to a higher proportion of slow responses reflected by the exponential part of an Ex-Gaussian distribution. Third, this exponential part was linked to a measure of work capability.

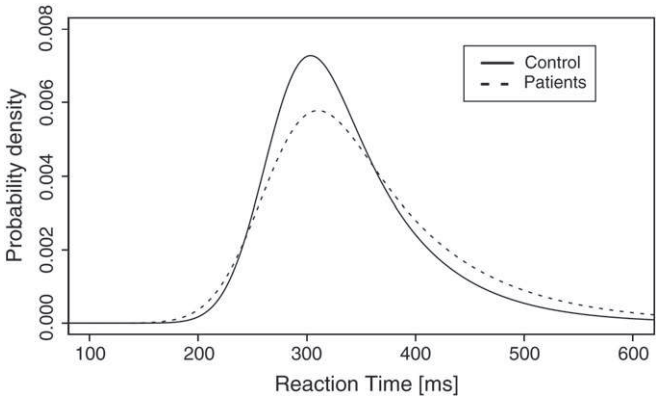

Fig. 1. Probability density distribution based on the estimated Ex-Gaussian parameters for patients with schizophrenia and healthy controls.

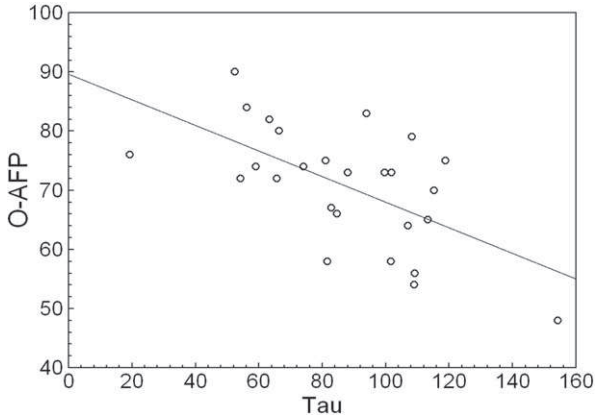

Fig. 2. Association between tau (measure of right skewedness of reaction time data) and the O-AFP (evaluating work capability) within 26 patients with schizophrenia.

In a first step we intended to analyse whether in a high-functioning group of patients with schizophrenia and relatively preserved cognitive performance it is still possible to show a deficit in measures of IIV. Successful recruitment is supported by the fact that patients did not differ significantly from matched controls on premorbid intelligence, working memory scores and accuracy as well as mean reaction time measures. The only exceptions were a reduction in detection sensitivity in the Infrequent-Go condition and an increase in errors of omission in the CPT. In contrast, IIV differed consistently between groups with large effect sizes. This increase in short-term fluctuations of reaction time was also observed in the Frequent-Go condition, where d' did not differentiate between groups, therefore indicating a fundamental deficit that occurs in every condition. Overall, this first analysis shows that IIV can be a valuable addition to conventional measures of task performance, capable of detecting differences between groups not apparent in other variables.

We performed additional analyses to address potential factors leading to an increased IIV. First, fatigue and practice might differentially affect healthy subjects and patients with schizophrenia. However, the only effect of time on task was found for the Infrequent-Go task, where control subjects slightly improved in the second run, while patients showed longer response times and higher variability. This suggests a modest benefit from practice in healthy subjects, which is not found in patients, who might suffer from fatigue effects on this specific task. Importantly, differences between groups were still significant in a separate analysis of the first run. Therefore, differences in IIV cannot be explained by effects of time on task. Second, the Go/Nogo task requires switches between target and non-target trials. Therefore, commonly observed impairments in cognitive flexibility might have contributed to the increased IIV in patients. However, switch costs did not differ significantly between groups. Overall, there might be a small modulation of IIV by time on task on certain tasks, but the strong increase in IIV in patients with schizophrenia cannot be reduced to effects of time on task or cognitive inflexibility.

In a second step we analysed the data of the Frequent-Go condition regarding the underlying reaction time distribution. We asked whether the distribution allowed further conclusions about the kind of impairment that expresses itself in higher IIV. An Ex-Gaussian distribution provided a good fit with the reaction time data. Regarding the estimated parameters only tau was significantly different between the two groups. Mu and sigma, representing the normal part of the distribution, were comparable in both groups. Therefore the slope on the left side of the distribution did not differ compared to controls, meaning that the fast responses did not differ between groups. Differences were restricted to the exponential part of the distribution,

comprised in the diminished height and the more right skewed probability density function. Therefore, patients with schizophrenia with limited cognitive impairment are able to process information as quick as healthy controls. A similar pattern has been found in some but not all studies with more severely impaired patients (Belin and Rubin, 1995; Birkett et al., 2007; Kaiser et al., 2008).

To address these differences we performed an exploratory analysis to address the impact of illness duration and symptoms. No significant correlations between Ex-Gaussian parameters and positive or negative symptoms were found. This suggests that the observed changes in reaction time distribution are largely independent from current symptoms, although the low symptom load limits the interpretation of this finding. Illness duration was found to be associated with an increased mu, i.e. a right shift of the mean of the normal part of the distribution. In contrast the increased tau, i.e. the right-skew of the distribution, was not affected by illness duration. This suggests that the increase in single trials with very slow reaction times might reflect a core feature of schizophrenia present at all stages of the disorder. In contrast, the additional overall slowing associated with longer illness duration does not seem to be a stable marker, although this interpretation is limited by the relatively short illness duration in our study group. It could reflect progressive brain changes not present at illness onset or continued exposure to antipsychotic drug treatment. In any case, higher IIV in our sample is not due to an unsystematic dispersion on both ends of the distribution, but arises from the right end of the distribution, caused by a greater proportion of abnormally slow responses. Furthermore, a more right-skewed distribution implies that the common findings of generally slowed reaction times in patients with schizophrenia might be partly due to an instability of response systems rather than consistent and inherent slowness.

A similar pattern in IIV has been found in children with ADHD (Leth-Steensen et al., 2000; Klein et al., 2006) and it has been suggested that both disorders share a common neurodevelopmental component (Oie and Rund, 1999). Regarding the neurophysiological basis of increased IIV the question can be raised whether the different concepts invoking an instability of information processing could not be fruitfully applied to both disorders. First, this regards the concept of an increase in prefrontal noise. As a common pathway a reduction in prefrontal dopamine transmission, which occurs in schizophrenia and ADHD, can lead to reduced activity at prefrontal D1 receptors, which is the main mechanism thought to underly the increase in cortical noise (Winterer and Weinberger, 2004; Arnsten, 2006). Second, cerebellar dysfunction as a key feature of cognitive dysmetria has been observed in both disorders (Andreasen et al., 1998; Valera et al., 2007). This has mainly been addressed in structural as well as functional neuroimaging studies. Importantly, increased IIV in schizophrenia has also been found on an eyeblink conditioning task, which relies mainly on the integrity of the cerebellum and not the prefrontal cortex (Brown et al., 2005). Thus, increased IIV can potentially be related to comparable disturbances in fronto-cerebellar circuits in schizophrenia and ADHD. Accordingly both disorders are associated with attentional and executive dysfunction as well as motor abnormalities (Chen et al., 2001; Klimkeit et al., 2005).

However, despite these commonalities ADHD and schizophrenia are very different disorders regarding symptoms, development and course of the illness. Differences might in part be explained by different dysfunctions within fronto-cerebellar circuits. For example, in their computational model of prefrontal cortical function, Rolls et al. (2008) suggest that schizophrenia is associated with a reduced stability in the high-firing state leading to a loss of stable representations and cognitive deficits. This pattern could also be related to ADHD, while positive symptoms are caused by an additional loss of stability in the spontaneous low-firing state, which might be specific to schizophrenia. However, any account for the differences between these two disorders almost certainly has to include differential affection of other brain regions. The most promising avenue to integrate these different approaches might be a stronger focus on different patterns of disturbed brain development in these disorders (Toga et al., 2006).

An alternative explanation not primarily invoking instability of information processing on a neurophysiological level would view increased IIV as resulting from an impairment of attentional control associated with lesions to the prefrontal cortex regardless of their cause. This view is supported by studies showing higher IIV after lesions to the prefrontal cortex (Stuss et al., 2003; Picton et al., 2007). In order to more specifically address this question it would be important to perform quantitative modelling of reaction time distributions in these patient groups, ideally in direct comparison with schizophrenia and ADHD.

In a third step we calculated the correlation between tau and the O-AFP, a measure of work performance. We found a significant negative correlation indicating that a more right skewed distribution with a greater amount of slow responses was associated with a lower working capability. Intra-individual standard deviation showed a similar but less pronounced correlation with work capability on all three task conditions. These findings confirm and expand the results from Wexler and Nicholls (2004). It clearly shows that not variability or slowing in general, but an increase in slow responses on a relatively simple reaction time task is specifically linked to work capability. This supports the view of this parameter as a clinically relevant measure of a core dysfunction. In addition, further research is needed to determine whether IIV is a suitable longitudinal predictor and can be fruitfully employed in treatment studies with medication and cognitive remediation.

In summary, IIV in general and the slow end of the reaction time in particular differentiate high-functioning patients with schizophrenia from controls with higher effect size than other measures of cognitive functioning. Future research will have to decide whether this reflects a core deficit in the stability of information processing on a neurophysiological level or just a highly sensitive measure of a deficit in attentional control, which can be caused by a variety of lesions to the prefrontal cortex. Aside from providing a potential behavioural measure for neurophysiologic deficits underlying schizophrenia, measurements of IIV can be linked to real-world performance and should be further investigated for clinical use.

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Temporal variability and spatial diffusion of the N2 event-related potential in high-functioning patients with schizophrenia

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ABSTRACT

Recent theories of schizophrenia have proposed a fundamental instability of information processing on a neurophysiological level, which can be measured as an increase in latency variability of event-related potentials (ERPs). If this reflects a fundamental deficit of the schizophrenic illness, it should also occur in high-functioning patients. These patients have also been observed to show a more diffuse activation pattern in neuroimaging studies, which is thought to reflect compensatory processes to maintain task performance. In the present study we investigated temporal variability and spatial diffusion of the visual N2 component in a group of high-functioning patients with preserved cognitive performance. 28 patients with schizophrenia and 28 control participants matched for gender, age and education participated in the study. Subjects performed a visual Go/Nogo task, while event-related potentials were obtained. Trial-to-trial latency variability was calculated with a Wavelet-based method. Patients with schizophrenia showed a robust increase in N2 latency variability at electrodes Fz and Cz in all task conditions. Regarding spatial distribution healthy participants showed a focused fronto-central N2 peak. In contrast, patients with schizophrenia showed a more diffuse pattern and additional negative peaks over lateral electrodes in the Nogo condition. These results clearly show that even in high-functioning patients with schizophrenia a higher temporal variability of ERPs can be observed. This provides support for temporal instability of information processing as a fundamental deficit associated with schizophrenia. The more diffuse scalp distribution might reflect processes that compensate for this instability when cognitive control is required.

1. Introduction

Influential models on the neurophysiology of schizophrenia emphasize an instability of information processing in the brain (Andreasen et al., 1998; Tan et al., 2007; Rolls et al., 2008). Winterer and others have suggested an increase in noise in frontal cortical networks in schizophrenia, which has been supported by electrophysiological and functional imaging data (Winterer and Weinberger, 2004). A putative measure of temporal instability of information processing is latency variability of single-trial event-related potentials (ERPs), which has been suggested to be the time-domain equivalent of decreased signal-to-noise ratio (Makeig et al., 2002; Winterer et al., 2004).

Patients with chronic schizophrenia show increased latency variability of the P3 event-related potential component (Ford et al., 1994; Roth et al., 2007). However, if this phenomenon represents a fundamental deficit associated with schizophrenia, one would expect it to occur even in high-functioning patients, who show little or no cognitive impairment. This type of population has not yet been the focus of studies addressing event-related potential variability. The response instability in schizophrenia has been proposed to lead to an inefficient neural response to cognitive demands (Tan et al., 2007). If this instability can be observed in high-functioning patients, this raises the question how they manage to preserve task performance despite the inefficient neural response. One line of argument is inspired by brain imaging studies of patients with preserved task performance. These patients commonly show areas of increased activation in particular in the prefrontal cortex, but also in other brain areas (Manoach et al., 2000; Kim et al., 2010). This pattern of spatial diffusion has been interpreted as recruitment of additional networks to compensate for the underlying inefficiency (Tan et al., 2007). Despite the putative link between temporal and spatial diffusion of

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neurophysiologic responses, these phenomena have to our knowledge not been addressed within one study.

In the present study we conjointly addressed latency variability and spatial distribution of the N2 component of the event-related potential. We focused on this component, because it is sensitive to requirements for cognitive control and has been consistently shown to be abnormal in patients with schizophrenia. The anterior N2 component is a negative deflection in the ERP that occurs between 150 and 400 ms after a stimulus over fronto-central electrodes close to the midline (Folstein and Van Petten, 2008). It can be observed in classic oddball paradigms requiring target detection, but is usually larger when cognitive control is required. A prominent example is the Nogo-N2 observed after a stimulus that requires inhibition of a prepotent response (Falkenstein et al., 1999; Kaiser et al., 2006). Reduced negativity in the N2 region is a robust abnormality in schizophrenia present in a variety of tasks (O'Donnell et al., 1993; Egan et al., 1994; Bruder et al., 1998; Brown et al., 2002; Umbricht et al., 2006). Single-trial variability of the N2 component has to our knowledge not been addressed in patients with schizophrenia.

Thus, we obtained event-related potentials in a Go/Nogo task to conjointly address latency variability and spatial distribution of the N2 component. For this purpose we recruited a sample of high-functioning patients with schizophrenia who showed little cognitive impairment. The study hypotheses were:

(1) Patients with schizophrenia show increased latency variability of the N2 component in comparison to healthy controls despite preserved task performance
(2) Patients with schizophrenia show a more diffuse spatial distribution of the N2 component in comparison to healthy controls
(3) Latency variability and spatial diffusion are positively correlated in patients with schizophrenia

2. Materials and methods

2.1. Participants

We recruited 28 right-handed inpatients satisfying DSM-IV criteria for schizophrenia or schizoaffective disorder confirmed by diagnostic interview (M.I.N.I., Sheehan et al., 1998). We excluded any patient with another Axis I disorder, substance abuse in the last 2 months or neurological problems. Patients were rated on the PANSS (Kay et al., 1989) by a trained psychologist and all patients with any positive symptom rated higher than four were excluded. The study was carried out in accordance with the Declaration of Helsinki and approved by the local institutional review board. All patients gave written informed consent.

For demographic and clinical characteristics of the patient sample see Table 1. All patients were medicated with atypical antipsychotics. Five patients were additionally treated with antidepressive medication and one with a mood stabilizer. Patients were admitted to participate in the preparation for a demanding rehabilitation program including professional training. There were no strict selection criteria for entering the program, but patients had to be considered suitable for work rehabilitation by the referring physicians. Therefore, this group was expected to represent a high-functioning population, which was confirmed by neuropsychological testing (see Table 2). After admission patients participated in a three week assessment and preparation period, during which the study was conducted.

We further recruited 28 right-handed healthy controls from hospital staff matched for gender, age and years of education. They were screened with the M.I.N.I. for Axis I disorders, which were exclusion criteria.

2.2. Task and procedure

In an uncued Go/Nogo task participants were required to answer as fast and correctly as possible by pressing the left mouse button to a visual target stimulus (see Fig. 1). To a second non-target visual stimulus, no reaction was required. At the beginning of each block, participants were informed whether the target would occur infrequently (Go condition) or frequently (Nogo condition). In the Go condition the stimulus requiring response occurred in 20% of trials. In the Nogo condition the stimulus requiring response occurred in 80% of trials. The high frequency leads to a prepotent motor response, which has to be inhibited on the remaining 20% of trials. Within a trial the stimulus was presented for 120 ms followed by a fixation cross for 1340 ms. The sequence of trials within each block was pseudorandomized and no more than two rare events occurred in direct sequence. In each of the two runs we used a mixed sequence of 4 Go and 4 Nogo blocks of 40 trials, separated by a short break. Each run had a duration of 8 min and 26 s.

2.3. Behavioral data acquisition and analysis

Participants' responses were recorded with the stimulation computer using the Presentation software. During the Go/Nogo task, reaction times and errors were registered. Behavioral variables (reaction times and errors) were entered as a dependent variable in a mixed ANOVA with the factors group and condition. Statistical analysis of behavioral and EEG data was performed with Statistica (Statsoft Inc., Tulsa). Significance level was set to $p<0.05$.

Table 1
Group characteristics of healthy controls and participants with schizophrenia.

	Healthy controls	Patients with schizophrenia	t-value (df = 54)	P
Group characteristics				
Age	25.50 (9.40)	26.07 (6.90)	−0.26	0.80
Years of education	14.40 (2.60)	14.32 (2.70)	0.03	0.98
Male/female	20/8	20/8		
PANSS positive		12.79 (2.96)		
PANSS negative		18.43 (4.69)		
PANSS global		32.50 (5.67)		
Illness duration (yrs)		3.11 (2.36)		
Verbal intelligence				
MWT-B raw score	27.21 (5.20)	27.86 (4.17)	−0.51	0.61
MWT-B estimated IQ	103.25 (12.18)	103.61 (10.20)	−0.11	0.91

Table 2
Behavioral data for the Go/Nogo task and additional neuropsychological tests.

	Healthy controls	Patients with schizophrenia	t-value (df = 54)	P
Go condition				
Mean RT (s)	426.79 (46.98)	459.39 (73.31)	−1.98	0.053
Errors of omission (%)	0.50 (1.54)	1.90 (4.89)	−1.44	0.16
Errors of commission(%)	0.45 (0.46)	0.73 (0.77)	−1.64	0.11
Nogo condition				
Mean RT (s)	341.09 (45.11)	362.80 (63.09)	−1.48	0.14
Errors of omission (%)	1.00 (1.39)	1.62 (3.05)	−0.97	0.34
Errors of commission (%)	12.89 (10.49)	17.52 (11.94)	−1.54	0.13
Working memory				
Digit span forward	9.46 (1.91)	9.30 (2.11)	0.31	0.76
Digit span backward	7.00 (2.14)	6.33 (2.20)	1.14	0.26
Letter number sequencing	11.36 (2.83)	10.67 (2.54)	0.95	0.35
Corsi forward	8.93 (1.65)	8.81 (1.77)	0.25	0.81
Corsi backward	8.86 (2.07)	8.07 (1.64)	1.55	0.13

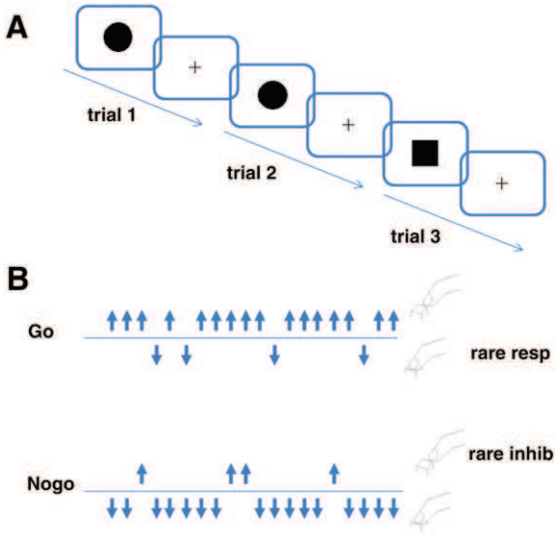

Fig. 1. Go/Nogo task with two conditions. In the Go condition a rare response is required to the 20% infrequent stimuli. In contrast, in the Nogo condition an inhibition was required, when an infrequent stimulus occurred. Electrophysiological responses to the infrequent stimuli were subject of the analyses presented.

2.4. EEG data acquisition and preprocessing

Scalp voltages were collected using a 35-channel Easy Cap (Falk Minow Systems, Germany). The reference electrode was placed between Fz and Cz, the ground electrode attached near the sternum. We selected a vertex reference electrode for recording, because it was used successfully in our previous Go/Nogo studies with patient populations and yields a low risk of reference artifacts (Kaiser et al., 2003; Roth et al., 2007). Additionally, eye movements were monitored with supra- and infraorbital electrodes and with electrodes on the external canthi. Electrode impedance was maintained below 5 kΩ for all recordings. Electrical signals were recorded with Brainamp amplifier (bandwidth DC 250 Hz, no notch filter) and digitized (sampling rate 500 Hz). The EEG data were preprocessed using the BrainVision Analyzer Software. The continuous EEG was segmented into epochs starting 100 ms before the stimulus and lasting until 1200 ms after stimulus onset, it then was baseline corrected over the 100 ms prestimulus epoch. Eye movement artifacts were removed by employing the algorithm by Gratton and Coles (Gratton et al., 1983) and all trials were semiautomatically screened for remaining artifacts. Finally, an average reference transform was applied. The average reference provides probably the least biased of possible references and also allows activity at or close to the original reference site to be displayed (Dien, 1998).

2.5. EEG data analysis

2.5.1. Average ERPs

Average ERPs were calculated for each participant and condition using Brain Vision Analyzer (Brain Products Inc., Munich). The focus of the present study was the anterior N2 component, which is most prominent at fronto-central midline electrodes. We therefore focused on electrodes Fz and Cz. We extracted individual peak latencies and mean amplitudes for the time window 240–300 ms. This time window covered the N2 component for both groups and conditions. Latency and amplitude were entered as a dependent variable into a mixed ANOVA with factors group and condition separately for electrodes Fz and Cz.

2.5.2. Single-trial analysis — latency and amplitude variability

Analysis of single-trial data relied on the EEGlab data structure and custom MATLAB scripts, which can be obtained by contacting the corresponding author. We used multiresolution wavelet analysis in order to decompose the single-trial data into different scales which correspond to different frequency bands (for details see (Roth et al., 2007). The wavelet decomposition of the original signal corresponds to multiple application of bandpassfiltering steps. These bandpassfilters have some desirable properties for processing of single-trial ERPs. They are linear phase filters, which is important for estimating time delays of an ERP component. Furthermore, the filters are localized near optimal in the time and frequency domain (Quian Quiroga, 2000). Another characteristic of the b-spline wavelet is its compact support which means that it can be implemented by a filter with finite impulse response (FIR).

As delta and theta frequencies account for the generation of the N2 component (Karakas et al., 2000), the signal was reduced to these frequency bands by setting the wavelet coefficients of the other frequency bands to zero in order to facilitate the identification of the N2 peak in the single trials. Single-trial peaks were determined subsequently by selecting the local negative maximum in the sum of the delta and theta band in the selected time window (190–400 ms). If there was only an absolute maximum but no local maximum (real peak) in this time window the trial was discarded from the analysis. For the selected single-trial peaks we extracted latency and amplitude. Latency and amplitude variability were defined as standard deviations of the individual single-trial values.

2.5.3. Spatial distribution of the N2 component

The first step was to analyze spatial diffusion on a group level. For spatial analyses the time window between 240 and 300 ms was used. To assess spatial distribution across frontal electrodes we conducted a mixed ANOVA with mean voltage as dependent variable and the factors group and electrode (F11, F7, F3, Fz, F4, F8, and F12). This procedure does not allow distinguishing between spatial diffusion resulting from higher inter-individual variability in the patient group and more diffuse distribution on an individual level. Therefore, we calculated an individual diffusion index by subtracting lateral from medial frontal amplitudes: $((Fz-F7)+(Fz-F8))/2$. The more negative this index the more focused the individual N2. The more these differences tend to zero the more wide-spread the activation. This spatial diffusion index was then compared between groups with a two-sample *t*-test.

3. Results

3.1. Behavioral data

Patients with schizophrenia did not differ significantly from healthy controls in mean reaction time or in error rates (see Table 2). A more detailed analysis of the performance in the Go/Nogo task in relation to other cognitive and outcome variables has been presented elsewhere (Rentrop et al., 2010).

3.2. N2 average event-related potential

3.2.1. Latency

Grand average ERPs are shown in Fig. 2. A mixed ANOVA for peak latencies with the factors group (schizophrenia/control) and condition (Go/Nogo) was performed separately for electrodes Fz and Cz. These analyses revealed no significant main effect or interaction involving group at Fz and Cz. Therefore we analyzed a common N2-time window (240–300 ms) for both groups.

3.2.2. Amplitude

In order to analyze differences in amplitude, a mixed ANOVA with group and condition was performed for Fz and Cz separately. At Fz the ANOVA revealed a significant main effect of group ($F_{1,54}=9.95$, $p=0.003$), with patients with schizophrenia showing a smaller N2

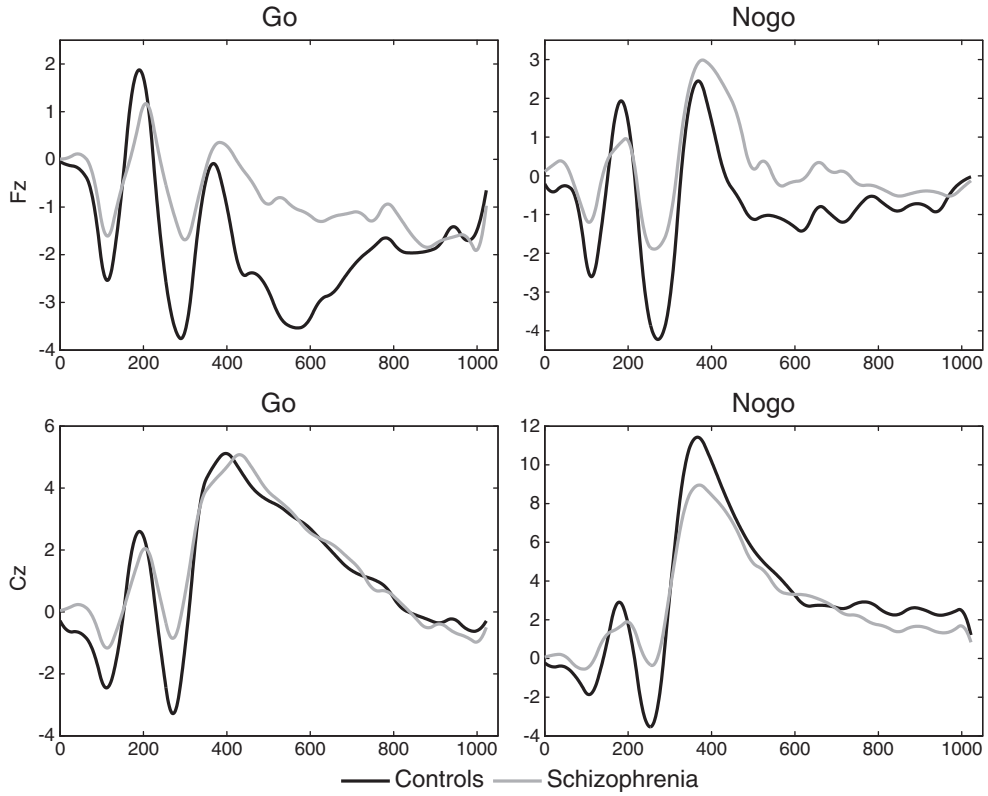

Fig. 2. Average event-related potentials in the Go/Nogo task at electrodes Fz and Cz. Go condition on the left, Nogo condition on the right.

amplitude (−0.79 μV) than controls (−2.56 μV). Comparably for Cz the main effect of group ($F_{1,54} = 19.83$, $p < 0.0001$) revealed a significantly smaller N2 amplitude (0.48 μV) for patients with schizophrenia compared to the control group (−1.29 μV). In both analyses the condition × group interaction effect was not significant.

3.3. N2 single-trial analysis — latency and amplitude variability

3.3.1. Drop-out rates

Mean percentage of excluded trials was low and did not differ significantly between groups (schizophrenia: 4%, control: 3%).

3.3.2. Single-trial latency variability

A mixed ANOVA with the factors group and condition was performed for Fz and Cz separately (see Table 3). For both electrodes the factor group was significant, which reflects increased N2 single-trial latency variability in patients with schizophrenia. The condition × group interaction was not significant indicating that this effect occurred in both conditions. The enhanced variability of the N2 latency in patients with schizophrenia is visualized in Fig. 3.

3.3.3. Single-trial mean amplitude and amplitude variability

A mixed ANOVA with the factors group and condition was performed for mean single-trial amplitude and amplitude variability (see Table 3). There was no main effect or interaction involving group for mean single-trial amplitude at Fz indicating no significant differences between groups. However, at Cz there was a main effect of group indicating reduced mean single-trial amplitude in patients with schizophrenia. There was no condition × group interaction. Furthermore, there were no significant effects involving group for single-trial N2 amplitude variability at any electrode.

Table 3
Results of N2 single-trial analysis. Significant effects in bold font.

	Healthy controls		Patients with schizophrenia		Main effect group		Interaction condition × group	
	Go	Nogo	Go	Nogo	F(1,54)	*p*	F(1,54)	*p*
Latency variability								
Fz	45.91 (7.64)	41.13 (8.81)	49.57 (7.34)	46.42 (9.16)	**5.40**	**0.02**	0.56	0.46
Cz	41.22 (6.36)	37.75 (11.04)	47.82 (7.04)	46.81 (10.98)	**14.34**	**0.0004**	0.91	0.34
Mean amplitude								
Fz	−6.78 (3.32)	−7.08 (3.08)	−5.92 (2.86)	−5.75 (3.09)	1.94	0.17	0.87	0.36
Cz	−6.24 (2.70)	−6.39 (3.50)	−4.24 (2.76)	−4.21 (2.37)	**9.20**	**0.004**	0.07	0.79
Amplitude variability								
Fz	6.61 (1.61)	6.52 (1.69)	6.60 (2.54)	6.44 (2.03)	0.01	0.93	0.06	0.80
Cz	7.46 (2.54)	7.89 (2.51)	6.31 (1.50)	7.09 (1.82)	3.22	0.08	0.90	0.35

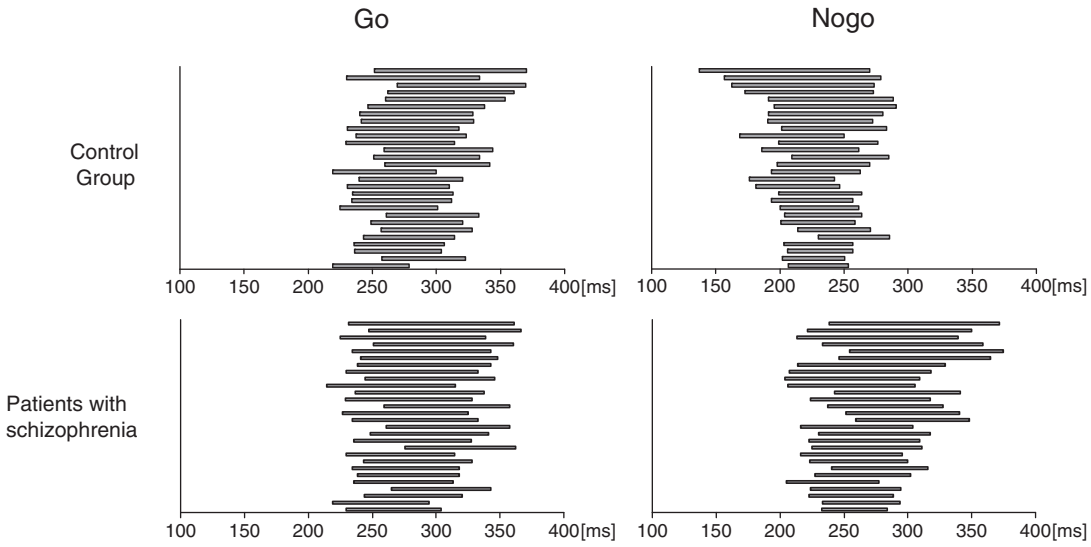

Fig. 3. Single-trial latency variability at Cz of the N2 component in the Nogo condition of 28 patients with schizophrenia and 28 healthy controls, showing the individual mean single-trial latency ± the intra-individual standard deviation in ms.

3.4. Spatial distribution of the N2 component

3.4.1. Group level

To assess spatial distribution we performed mixed ANOVAs for each condition with the factors group and electrode (F11, F7, F3, Fz, F4, F8, and F12). For the Go condition there was no main effect of group. However, the group × electrode interaction was significant ($F_{1,54} = 10.87$; $p < 0.0001$), therefore confirming the visual impression that the activation pattern differed significantly between the two groups (see Fig. 4A). To compare the extent of lateral activation between groups, we performed two-sample t-tests for electrodes F11 and F12. At electrode F11 there was trend towards a larger negativity in patients with schizophrenia ($t_{54} = 1.8$, $p = 0.08$). At F12 there was no significant difference. In the Nogo condition there was also no significant main effect of group, but a significant group × electrode interaction ($F_{1,54} = 14.31$; $p < 0.0001$) (see Fig. 4B). At electrode F11 patients with schizophrenia showed a significantly more negative amplitude than control subjects ($t_{54} = 2.67$, $p = 0.01$). At F12 a similar effect was observed at a trend level ($t_{54} = 1.92$, $p = 0.06$).

3.4.2. Individual level

A student *t*-test comparing the individual diffusion index between groups was highly significant (Go: $t_{54} = 4.56$, $p < 0.0001$; Nogo: $t_{54} = 4.60$, $p < 0.0001$), which indicates a more diffuse activation pattern in patients with schizophrenia on the individual level.

3.5. Relationship between latency variability and spatial diffusion

We calculated Pearson correlations between latency variability and the individual diffusion index for the patient group. In the Go condition there was no significant correlation at Fz or Cz. In contrast, in the Nogo condition we found a highly significant correlation between latency variability and the individual diffusion index at both electrodes Fz ($r = 0.48$, $p = 0.01$) and Cz ($r = 0.56$, $p < 0.01$).

3.6. Analysis of the P3a component

Although not the main focus of the paper we present results for the P3a component regarding average event-related potentials and single-trial analysis. All subsequent results concern electrode Cz, where the P3a peak was most prominent.

3.6.1. Average event-related potential

A mixed ANOVA with the factor group and condition for P3 latency did not reveal a main effect or interaction involving group. Therefore, for the analysis of mean amplitude we selected a common time window 340–430 ms. The ANOVA for mean amplitude did not show a significant main effect or interaction involving group.

3.6.2. Single-trial analysis

A mixed ANOVA with the factors group and condition was performed for latency variability, mean single-trial amplitude and amplitude variability. One patient with schizophrenia was excluded, because single-trial latency variability differed more than three standard deviations from the mean. For latency variability there was a trend towards a main effect of group ($F_{1,53} = 2.89$, $p = 0.09$), which suggests that patients with schizophrenia had higher individual standard deviation than controls (71.67 ms vs. 67.13 ms). There was no group × condition interaction. For mean single-trial amplitude and amplitude variability there was no main effect or interaction involving the factor group.

4. Discussion

The main findings of the present study are an increased latency variability of the anterior N2 component and a more diffuse spatial distribution of the N2 component, when cognitive control is required. Additionally, correlational analysis suggests a link between these phenomena. Importantly, these findings were obtained in a high-functioning group of patients with schizophrenia who show relatively preserved task performance.

The first main finding of the study is the robust increase in latency variability of the anterior N2 component in the patient group. Importantly, our wavelet-based method allowed identifying peaks in a high percentage of single trials in both groups. The lack of differences between groups is important, because the standard deviation of single-trial latencies also depends on the number of included trials. The increase in N2 latency variability was consistently observed across conditions and seems to be independent of the inhibitory requirements in the Nogo condition. We also observed a trend towards an increased P3a latency variability in patients with schizophrenia. Thus, the present findings complement previous results of increased latency jitter and decreased signal-to-noise ratio over frontal electrodes in oddball tasks (Ford et al.,

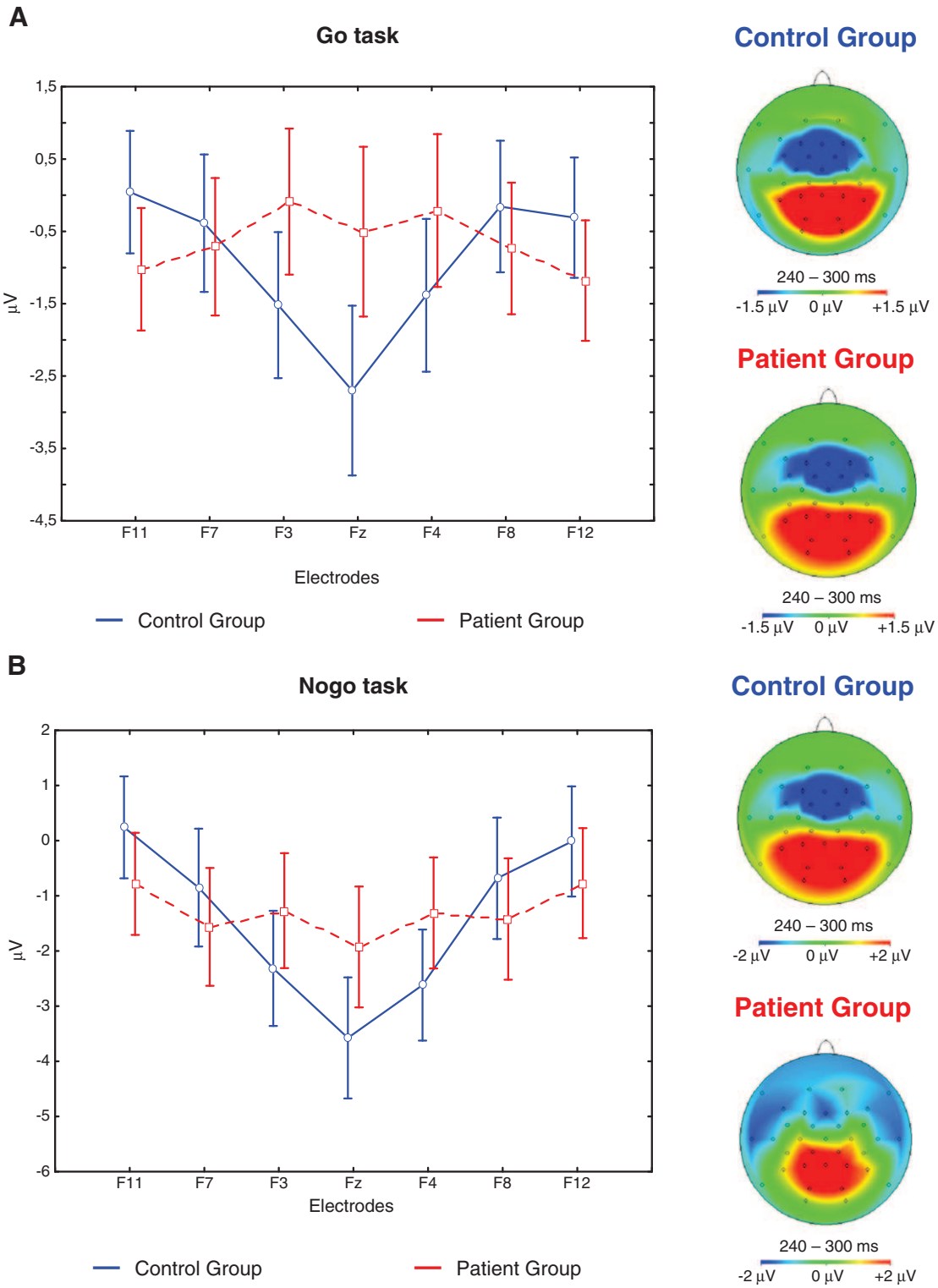

Fig. 4. Spatial distribution in the N2 time window (240–300 ms) in the (A) Go condition and (B) Nogo condition. On the left side mean amplitudes including standard deviation for patients with schizophrenia (red squares) and controls (blue circles) across the frontal electrode line. The right side of the figure shows topographical maps of the mean amplitude in the N2 time window.

1994; Winterer et al., 2004; Roth et al., 2007). They are also consistent with the finding of reduced trial-to-trial phase coherence in patients with schizophrenia (Ford et al., 2008). In contrast to these previous studies we recruited a high-functioning sample with relatively short illness duration. Importantly, performance on the Go/Nogo task and accompanying working memory tasks was not impaired in this group.

Thus, the increased latency jitter might represent a fundamental neurophysiological deficit in patients with schizophrenia, which is the subject of intense discussion. Approaches drawing on computational neuroscience have proposed that randomly spiking neurons lead to an increase in noise and increased trial-to-trial variation in postsynaptic potentials (Rolls et al., 2008). An imbalance between dopamine D1

and D2 receptors has been considered to account for this effect on the molecular level (Winterer and Weinberger, 2004). This dopaminergic modulation interacts with glutamatergic and GABAergic systems. Regardless of the molecular mechanism the result is a fundamental instability in prefrontal microcircuits that is considered to be characteristic of the schizophrenic illness.

It is an interesting question how our patients managed to preserve task performance despite this fundamental deficit. Related to this question, we observed no association between error rates and single-trial variability. In other words our patients show decreased response stability on an electrophysiological level, but this does not seem to affect task performance. This observation is in contrast with previous studies addressing single-trial variability or signal-to-noise ratio in more severely impaired patients, which showed an association with task performance (Winterer et al., 2004; Roth et al., 2007). It can be argued that patients with preserved task performance compensate their inefficient processing by recruiting additional brain networks or additional regions within the same network (Tan et al., 2007; Kim et al., 2010).

Therefore, we addressed the spatial distribution of the N2 component. In both conditions patients showed a reduced fronto-central N2, which has been previously reported for oddball tasks (Bruder et al., 1998; Potts et al., 2002). Importantly, they showed additional activation over lateral frontal electrodes in the Nogo condition, i.e. a more diffuse spatial distribution of the N2 component. We suggest that this spatial diffusion reflects compensatory recruitment of additional brain areas, in particular when cognitive control is required. In the Go condition, which corresponds to an auditory oddball paradigm, only a trend-level increase in negativity over left lateral electrodes was observed. Thus, our findings expand the respective observations by O'Donnell et al. (1993). In an auditory oddball task they found a flatter N2 gradient across the central electrode line, but no indication of additional lateral activation. Our findings suggest that in an oddball task compensatory spreading of the N2 is a rather small effect even in patients, who are able to preserve task performance. In contrast, the findings in the Nogo condition are more robust and emphasize that the compensatory activation depends on the task requirements. Moreover, our analyses show that this effect is not due to a larger between-subject-variability in the patient group, but that patients show a greater spatial diffusion of the N2 component on an individual level.

We further addressed the link between single-trial variability and spatial diffusion through correlational analysis. We found a highly significant correlation between these measures in the Nogo condition, but no significant correlation in the Go condition. These results provide additional evidence that compensation for the instability in information processing is mainly relevant in the Nogo condition. The Nogo condition is more difficult, which could per se require a higher degree of compensation. However, both groups show a specific increase in errors of commission in the Nogo condition. This suggests that the increased difficulty and compensatory activation are mainly due to an increased requirement for cognitive control.

In summary, our results show that schizophrenia is associated with higher temporal variability of ERPs even in high-functioning patients. This supports the concept that response instability in the prefrontal cortex is a fundamental deficit associated with the illness. Despite this processing inefficiency high-functioning patients are able to preserve task performance. When cognitive control is required, a more diffuse scalp distribution of ERPs reflects compensatory activation of additional brain regions.

Role of funding source

Funding of this study was provided by the German Federal Ministry of Education and Research (BMBF); the BMBF had no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Contributors

Stefan Kaiser and Matthias Weisbrod designed the study and wrote the protocol. Mirjam Rentrop and Katlehn Rodewald collected the data. Alexander Roth, Mirjam Rentrop, Stephan Walther, Joe Simon and Sibylle Metzler undertook the statistical analyses and prepared them for presentation. Mirjam Rentrop and Stefan Kaiser wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

All authors declare that they have no conflicts of interest.

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RESEARCH ARTICLE Open Access

Planning and problem-solving training for patients with schizophrenia: a randomized controlled trial

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Abstract

Background: The purpose of this study was to assess whether planning and problem-solving training is more effective in improving functional capacity in patients with schizophrenia than a training program addressing basic cognitive functions.

Methods: Eighty-nine patients with schizophrenia were randomly assigned either to a computer assisted training of planning and problem-solving or a training of basic cognition. Outcome variables included planning and problem-solving ability as well as functional capacity, which represents a proxy measure for functional outcome.

Results: Planning and problem-solving training improved one measure of planning and problem-solving more strongly than basic cognition training, while two other measures of planning did not show a differential effect. Participants in both groups improved over time in functional capacity. There was no differential effect of the interventions on functional capacity.

Conclusion: A differential effect of targeting specific cognitive functions on functional capacity could not be established. Small differences on cognitive outcome variables indicate a potential for differential effects. This will have to be addressed in further research including longer treatment programs and other settings.

Trial registration: ClinicalTrials.gov NCT00507988

Background

Cognitive deficits are important predictors of functional outcome in patients with schizophrenia [1,2]. This finding has motivated the development of different psychological treatment approaches to improve cognitive deficits, which have been subsumed under the term cognitive remediation [3]. There is now converging evidence that cognitive remediation has moderate effects on cognitive performance [4]. Importantly, these improvements can generalize to functional outcome, particularly when cognitive remediation is combined with comprehensive rehabilitation, such as vocational therapy (e.g. [5-8]).

Cognitive remediation covers a broad range of interventions that are heterogeneous with respect to a number of parameters. Importantly, there is considerable variation in the cognitive functions targeted in training programs. The dominant research focus in the 1980 s and 1990 s was on training procedures addressing a particular construct or even a specific task. Most prominently this included sustained attention based on findings in the Continuous Performance Test and executive function based on Wisconsin Card Sorting Test performance [9,10]. These studies were mostly focused on the question whether cognitive deficits can be remediated through training. Recently, more comprehensive training packages addressing a set of target functions have dominated the literature (e.g. [5,11]). This goes along with a shift in outcome measures. After many of the earlier studies sought to demonstrate improvement on the task trained, a broader effect on neuropsychological test performance has subsequently been considered a condition for improvement of patient

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relevant outcomes [12]. There is also a growing consensus that trials aimed at improving cognition should assess functional outcome directly or through an appropriate proxy measure [13]. Accordingly, functional outcome measures have been included in most recent trials of cognitive remediation (e.g. [14,15]).

Despite this rapidly developing body of research it is still a matter of discussion, which cognitive functions should be emphasized for successful cognitive remediation [16]. Interestingly, the earliest studies of cognitive remediation in schizophrenia have addressed this question to some extent. Wagner trained patients on a stimulus discrimination task with and without requirement for abstraction, but did not find a consistent advantage of one form of training [17]. Bellack and colleagues compared trained participants on either the Wisconsin Card Sorting Test or the Halstead Category Test. The authors could show that both groups improved on the non-trained test. However, these tasks involve strongly related cognitive operations and a differential effect on other cognitive functions was not the goal of the study [18]. Another line of research focused on strategies taught during training [19,20]. However, these latter studies have not included comparisons between training of different functions or tasks. Thus, it is still an open issue whether the training of certain specific functions is more effective than training of other functions. This question is pertinent in the clinical context, where therapists often employ a mix of training interventions adapted to setting and patients.

One strategy to approach this question is to relate change in specific cognitive functions to change in a functional outcome parameter. Recent studies have suggested that change in executive functions may best predict improvement in social or daily functioning and should thus receive emphasis in cognitive remediation [21,22]. Planning and problem-solving have received increased interest, because recent developments in the assessment of executive functions with high ecological validity have been applied to the study of patients with schizophrenia [23,24]. Interestingly, planning performance on tasks with real-world approximating interface and complexity has been associated with functional outcome and related proxy measures [25-27]. This includes overall performance on the naturalistic action test, community functioning and global assessment of functioning. These studies have suggested a particular role for planning and problem-solving in cognitive remediation, but have so far not provided direct evidence.

A more direct strategy to define target cognitive functions would employ head-to-head comparisons between training of specific cognitive functions. This approach could provide direct evidence for emphasizing specific cognitive functions over others. However, this type of comparison has only been conducted by Medalia and colleagues, who compared problem-solving training with memory training and treatment as usual in a sample of hospitalized patients with chronic schizophrenia [28]. Participants in the problem-solving remediation group worked under individual supervision with the software program *Where in the USA is Carmen Sandiego?* This educational software was selected, because it requires a range of problem-solving skills and was considered to promote intrinsic motivation. Patients who received ten sessions of problem-solving training showed greater improvement on problem-solving skills required for independent living. In contrast, patients receiving memory training did improve on the trained tasks, but not in functional outcome or executive functions [29]. Thus, this study provides direct evidence for a differential effect of different targets for intervention. However, the authors note important issues to be addressed in further research. First, it is an open question whether these findings in chronic inpatients can be generalized to less impaired patient groups. Second, final sample size was limited to less than twenty Participants in each treatment group. Third, it is an open issue whether their results pertain to the specific intervention or can be generalized to training of problem-solving in a broader sense.

Thus, the two approaches for defining the focus for cognitive remediation suggest executive functioning and more specifically planning and problem-solving as treatment targets. Planning and problem-solving can be conceived as higher executive functions, which require the integration of basic cognitive functions [30]. A crucial question is whether training of these higher-order functions strongly requiring integration provides an additional benefit over a training restricted to the basic cognitive functions (e.g. processing speed, attention, memory, lower-level executive functions). More generally, the present study addresses the question which level of cognitive functioning should be targeted.

In order to train patients on planning and problem-solving, we used the software package Plan-a-Day, which is based on an earlier concept by Funke und Krüger that has been adapted for psychiatric and neurologic patients [31]. In brief, participants are given a set of errands for one day that are described by location, time, action and importance. Participants have to interactively construct a plan for this set of errands, taking priorities and timing conflicts into account. The training can be delivered in individual and group format. In the present study, small groups of no more than five patients worked with the therapist. The comparison group trained on the basic cognitive functions processing speed, memory and attention/concentration, which have all been consistently shown to be impaired in patients

with schizophrenia [32,33]. These training tasks were carefully selected to not include planning and problem-solving components.

The aim of the study was to compare the effectiveness of two different approaches to cognitive remediation: targeting planning and problem-solving versus basic cognition. To our knowledge, this type of head-to-head comparison has not been performed for cognitive remediation in a rehabilitation setting. All patients received training parallel to a three-week inpatient work therapy, which was similar for all patients. We used a measure of functional capacity as a proxy measure for functional outcome. Functional capacity is assessed under standardized conditions and has been shown to be the most consistent predictor of functional outcome [2].

The study addressed two related research hypotheses:

(1) Planning and problem-solving training leads to stronger improvement of planning ability than training of basic cognition.

(2) Planning and problem-solving training leads to stronger improvement of functional capacity than training of basic cognition.

Methods

Study design

We carried out a single-blind randomized trial comparing planning and problem-solving training (Plan-a-Day) with training of basic cognitive functions (processing speed, attention, memory). Participants received the training interventions in an inpatient rehabilitation setting parallel to a three-week course of inpatient work therapy. Primary outcome was functional capacity and secondary outcome performance on tests of planning and problem-solving. The trial registration number at ClinicalTrials.gov is NCT00507988.

Participants

Participants were recruited from an inpatient rehabilitation unit at the psychiatric hospital, Karlsbad Langensteinbach, Germany. Before admission, patients were living in the community. They entered a treatment program aimed at facilitating return to work. This included patients with persistent problems after an acute illness episode as well as those with a longer illness course.

All patients entered the program as inpatients to allow intensive multimodal rehabilitation. During the initial three weeks all patients received a course of work therapy to identify strengths and weaknesses with respect to further rehabilitation and to start working on treatment targets with high priority. After this initial three week period an individual rehabilitation program was developed, which included further training and/or job searching. We chose to conduct the study during the initial three-week period, because the overall treatment program during this time period was similar for all patients and any confounding effects of other treatments in addition to the study intervention would be minimized.

Patients met the DSM-IV criteria for schizophrenia or schizoaffective disorder as confirmed by the MINI International Neuropsychiatric Interview [34]. Further inclusion criteria were (1) age between 18 and 45, (2) being in a non-acute phase of illness (defined by all PANSS positive items < 5), and (3) having an estimated IQ of 80 or above. Exclusion criteria were (1) diagnosis of a neurological disorder, (2) illicit substance use during the last month, and (3) a current comorbid Axis I disorder. Patients were enrolled in the study between August 2007 and February 2009.

Assessment

Planning and problem-solving

Planning ability was measured with a Tower of London analog (Planungstest; [35,36]) and the Zoo-Map subtest from the Behavioural Assessment of Dysexecutive Syndrome (BADS; [37,38]). Planning and problem-solving in complex scenarios was measured with a diagnostic version of Plan-a-Day [26]. This tool is a modified version of the training program (Figure 1). The diagnostic version employs a different user-interface and shorter scenarios in order to increase reliability. For diagnostic purposes, participants complete eight day plans, which take 30-45 minutes. The main scoring criterion is the total solution time. Internal consistency of the instrument has been found to be good (Cronbach's α = .78). Regarding construct validity, Plan-a-Day solution time shows significant correlations with the Tower of London and the Zoo-Map ($r = 0.42$, $r = 0.37$, both $p < 0.01$), but not with other neuropsychological tests. Importantly, Plan-a-Day contributes significantly to prediction of Global Assessment of Functioning scores, while other planning tests do not.

Functional capacity

Functional capacity was assessed with the Osnabruck Work Capabilities Profile (German: Osnabrücker Arbeitsfähigkeiten Profil, O-AFP; [39]), a 30-item inventory developed specifically for the purpose of assessing behaviour at work for persons with severe and persistent mental illness. The instrument was developed on the basis of the Work Personality Profile [40] with a stronger emphasis on easy application and sensitivity to change. The general labor market applies as a guiding principle for rating instructions. Using the O-AFP, the work therapist assessed functional capacity based on the patient's performance in work therapy at two time points, directly before the start of the intervention and directly after completion. The work therapist was trained in using the rating scale prior to the study. The

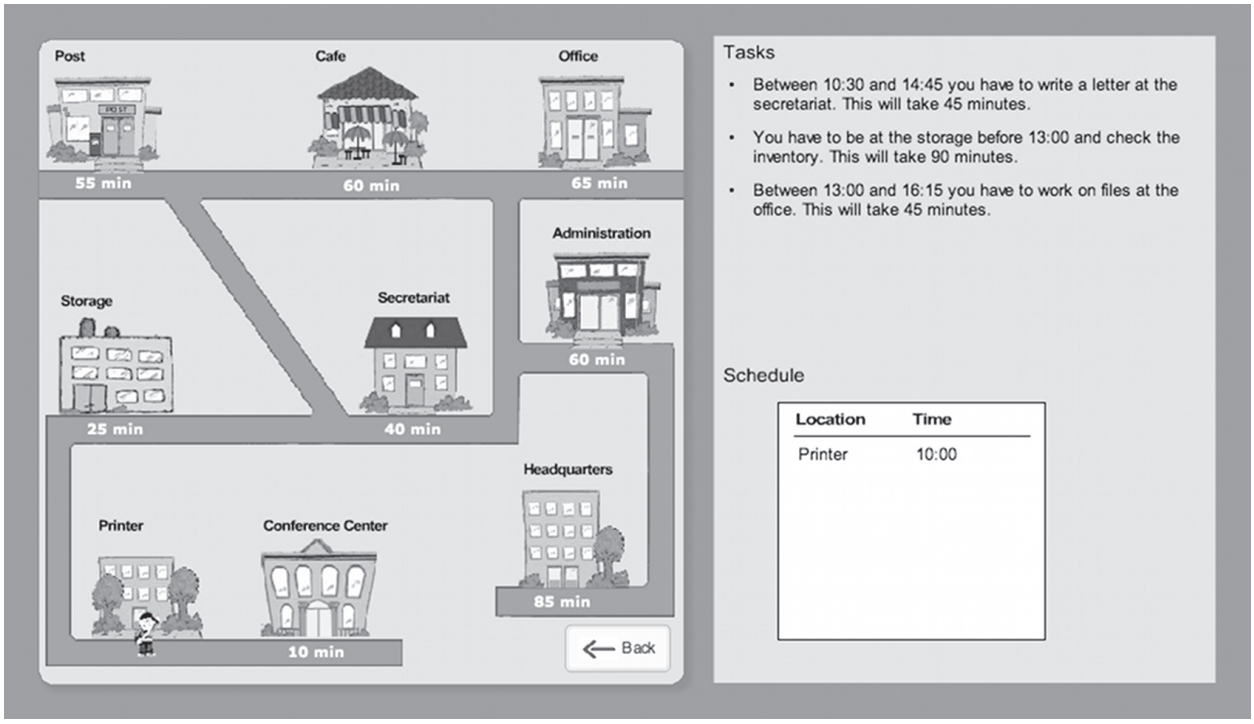

Figure 1 Plan-a-Day interface.

O-AFP consists of three scales: "Learning Ability" (ability to use instructions and to implement changes in the work plan when necessary), "Social Communication Ability" (ability to communicate with therapists and co-workers) and "Adaptation" (ability to work reliably and to adhere to rules). Each subscale includes ten items, which are rated on a four-point rating scale. The structure of the scale was confirmed by factor analysis based on a sample of 194 patients suffering from schizophrenia or schizoaffective disorder and are shown to possess good psychometric properties [39,41]. The internal consistency (Crohnbach's α) of the three subscales is high for learning ability (α = .94), social communication ability (α = .90) and for adaptation (α = .92).The inter-rater-reliability is good (r = .81). Since the subscale "learning ability" is most closely associated with cognitive functioning, it was selected as primary outcome measure. The total score was included as a secondary outcome measure.

Basic cognitive functions

Working memory was assessed with the digit forward, digit backward and letter-number sequencing subtests from the WAIS III [[42]] to assess verbal memory maintenance and manipulation [42]. The Corsi Block-Tapping Task was used to assess spatial working memory maintenance and manipulation, analogous to digit span forward and backward [43]. Trail Making Test and a single-trial Stroop Test were used to assess processing speed (TMT-A and reaction time Stroop neutral condition) and inhibition (TMT-B and reaction time Stroop incongruent-neutral condition) [44,45].

Premorbid intelligence was estimated through the Mehrfachwahl-Wortschatz-Intelligenztest MWT-B, a German analog of the National Adult Reading Test [46].

Symptoms

Symptoms were assessed by trained research psychologists using the Positive and Negative Syndrome Scale (PANSS; [47]).

Task motivation

After completion of the intervention, we assessed task motivation for the training program with the questionnaire to assess current motivation (German: Fragebogen zur Erfassung aktueller Motivation, FAM; [48]). This questionnaire includes four subscales: interest, challenge, probability of success and anxiety.

Interventions

Both groups

Participants were engaged in 10 training sessions of computer-based cognitive exercises either targeting planning and problem solving or basic cognition. The platform for all computer based exercises was the Reha-Com system (Hasomed GmbH, Germany). This program system includes several adaptive therapy procedures and

has been successfully used in cognitive remediation for patients with schizophrenia [49]. Following one individual introductory session, each session lasted 45 minutes and took place in a group of 3-5 participants, with participants usually completing three sessions per week for three weeks. Participants received a short introduction in every session and information about their progress after completing one session. As needed, participants received help during the training session.

Planning and problem-solving training

The training intervention with Plan-a-Day is based on a training concept originally developed by Kohler et al. [50]. It focuses on training participants to use a small set of simple but effective planning and decision-making heuristics (e.g. "most important tasks always first" or "maximize number or errands completed") that provide effective strategies for dealing with common goal-conflict situations in Plan-a-Day and everyday life. Increasing levels of difficulty are characterized for example by overlap between appointments, the difference between fixed and variable appointments as well as appointments, which cannot be included in the solution. In addition to computer exercises, patients included in the group working with Plan-a-Day participated in a transfer to everyday situations group. Topics in the group included, for example, work-therapy, planning shopping or planning appointments with public authorities.

Basic cognition training

This group trained three different tasks: (1) Processing speed: the task includes the presentation of visual stimuli that have to be responded to as quickly as possible. Increasing levels of difficulty were characterized by an increasing size of the stimulus set and progression from single to multiple choice reactions. (2) Attention and concentration: one picture shown separately has to be compared with and found among three to nine other pictures. Stimulus discriminability and set size increased with progression through levels. (3) Topological memory: the task is divided into two phases - acquisition and reproduction - of three to sixteen objects. Increasing levels of difficulty in the memory task were characterized by an increasing number of items to be retained. Patients were not instructed to use specific strategies for the basic cognition tasks.

Procedure

The study was carried out in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the University of Heidelberg Medical Faculty. All Participants gave written informed consent after the study had been fully explained. Participants were not paid for participation in the study. Following completion of the baseline assessments, participants were randomly assigned to one of the two training conditions by the project coordinator, who was not involved in the assessments or in the training procedure. Assessment of the primary outcome was blind to group allocation. All patients received work therapy parallel to the study interventions. Work therapy was conducted in a building separated from the setting of the cognitive interventions. Patients were instructed not to reveal their group allocation to the work therapist. Blinding for cognitive assessments could not be maintained in all cases.

Statistical analysis

First, we compared the groups at baseline on the demographic, clinical, and cognitive measures using t-tests (continuous variables) and Chi-Square analyses (categorical variables). Second, in order to evaluate changes over the treatment period in cognitive functioning and functional capacity, we performed mixed analysis of variance (ANOVA) with treatment group as between subject factor and time (baseline vs. 4-week assessment) as within subject factor. In cases of non-normal distribution, the variables were log-transformed.

SPSS, Version 16, was used for statistical analyses. All statistical tests were two-tailed, and significance was determined at the alpha 0.05 level. For all analyses related to the study's specific aim, effect sizes are reported using partial eta^2.

Results

Study flow

89 participants completed the baseline assessment and 77 (86.5%) completed the 4-week assessment. Participants completed an average of 8.42 (SD = 0.86) computer sessions. The Consort diagram is shown in Figure 2.

Comparison of groups at baseline

Statistical tests comparing patients assigned to Plan-a-Day or Basic Cognition indicated no significant differences in any demographic, diagnostic, or baseline clinical measures. Demographic and background characteristics for each group are summarized in Table 1. All patients were treated with atypical antipsychotics. Use of anticholinergic medication did not differ significantly between Plan-a-Day and Basic Cognition groups (7.9% vs 10.3%).

Regarding the level of functioning at the time of intake, the GAF scores indicated significant impairment (Table 1). However, in comparison with other studies of cognitive remediation, GAF scores in our sample were at the upper end of the range (e.g. [51,52]). The mean scores on cognitive test performance with available normative values (working memory tests and TMT) were within one standard deviation from the normative mean with the exception of TMT-B, which was between 1 and

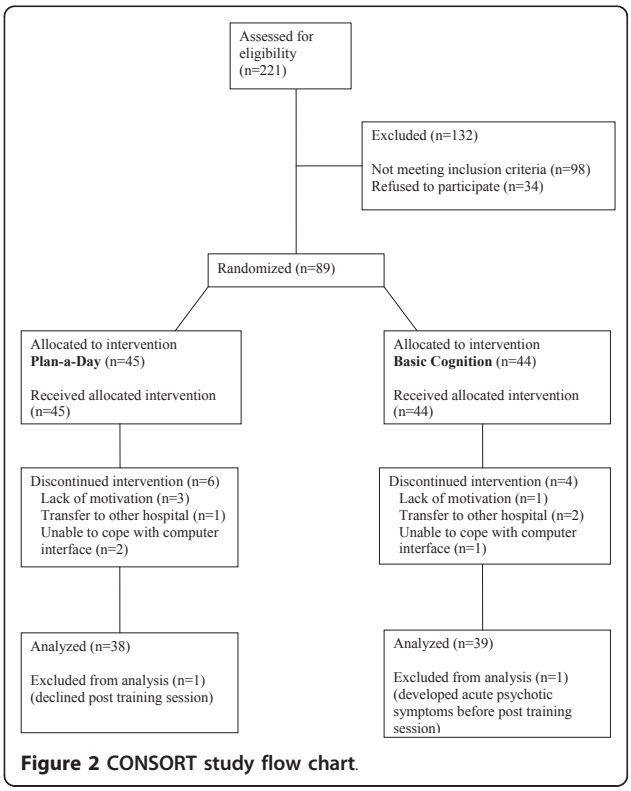

Figure 2 CONSORT study flow chart.

2 standard deviations from the normative mean. Overall, this suggests that most of the patients included had relatively mild cognitive impairment.

Outcomes

Outcomes are summarized in Tables 2 and 3.

Planning and problem-solving

The ANOVA revealed a main effect of time for Plan-a-Day "solution time" suggesting significant improvements across both groups ($F[1,75] = 71.66$, $p < .001$, $eta^2 = .49$). Importantly, a significant time × group interaction for Plan-a-Day "solution time" was found (Table 2), indicating stronger improvement in the planning and problem solving training group. Note that this effect remains significant at a Bonferroni-corrected threshold adjusting for the five test runs for the different outcomes.

For Planungstest "solution time" we observed a significant main effect of time ($F [1,75] = 7.66$, $p = .007$, $eta^2 = .093$) indicating improvement across both groups. There was no significant effect main effect for Zoo-Map "solution time". Importantly, there were no significant time × group interactions on Planungstest and Zoo-Map (Table 2).

Functional capacity

Analysis of change in scores for O-AFP learning ability subscale and total score did not show a significant time × group interaction, indicating a lack of significant differences between treatment groups (Table 2). A main effect of time was found for both variables ($F[1,75] = 111.97$, $p < .001$, $eta^2 = .599$ and $F[1,75] = 153.26$, $p < .001$, $eta^2 = .671$) indicating improvement in both groups during training. The numerical difference between pre- and post-training assessments was above the reliable change index cut-off for both variables (RCI learning ability = 4, RCI total score = 9).

Exploratory analysis - basic cognition

In an exploratory analysis, each of the nine tests of basic cognition was entered into a mixed-design ANOVA (Table 3). A significant time × group interaction was found only for reaction time in the neutral condition of the Stroop task ($F[1,69] = 8.22$, $p = .005$, $eta^2 = .11$) suggesting an advantage for basic cognition training.

Task motivation

There were no significant differences between groups on any subscale of the questionnaire used to assess training motivation (Table 1).

Progress over the course of training

To assess the progress of participants over the course of training, we provide the mean levels reached by the group at the end of the first and last training sessions. The Plan-a-Day group progressed from level 13 (range 6-25) to level 40 (range 31-54). The basic cognition group progressed over the course of the training as follows: Memory level 5 (range 2-8) to level 10 (range 3-16), attention level 6 (range 4-8) to level 16 (range 10-20) and processing speed level 2 (range 1-3) to level 10 (4-13).

Discussion

To our knowledge, this is the first study to compare cognitive remediation programs targeting specific cognitive functions in a rehabilitation setting. This comparison included a training of planning and problem-solving in contrast to a training of basic cognition. Overall, participants improved on cognitive performance and functional capacity. Planning and problem-solving training led to stronger improvement on one measure of planning and problem-solving, while basic cognition training had a stronger effect on one measure of processing speed. However, there was no differential effect between interventions on functional capacity. We discuss the effects observed in both training groups first and then focus on the differential effects between treatments as the main objective of the study.

Both groups improved on measures of cognitive functioning and functional capacity. We observed improvement in both patient groups in the learning ability

Table 1 Demographic and clinical characteristics of patients assigned to either Plan-a-Day or Basic Cognition

	Plan-a-Day (N = 38)		Basic Cognition (N = 39)		Test- statistic
Categorial Variables	**N**	**%**	**N**	**%**	**Chi-Square**
Gender					.65
Male	32	84.2	30	76,9	
Female	6	15.8	9	23.1	
Diagnoses					5.19
Schizophrenia, paranoid	27	71.1	30	76.9	
Schizophrenia, disorganized	1	2.6	0		
Schizophrenia, residual	2	5.3	0		
Schizophrenia, undifferentiated	1	2.6	0		
Schizoaffective disorder	5	13.2	9	23.1	
Schizophrenia simplex	2	5.3	0		
Occupational state					1.26
employed, on sick leave	13	34.2	18	46.1	
in academic or professional training, on sick leave	6	15.8	6	15.4	
unemployed	19	50	15	38.1	
ContinuousVariables	**Mean**	**(SD)**	**Mean**	**(SD)**	**t-statistic**
Age	28.03	7.04	29.46	7.42	-.87
Years of Education	14.68	2.96	15.55	3.71	-1.13
Premorbid IQ (MWT-B; raw score)	26.95	4.78	27.18	5.03	-.21
Age at 1st hospitalization	23.03	6.28	25.70	7.05	-1.76
Global Assessment of Functioning	60.00	6.88	60.05	6.33	-.03
Baseline PANSS Total	62.03	8.72	63.79	12.57	-.72
3-week PANSS Total	54.61	7.99	56.46	9.89	-.90
QCM: challenge	20.74	3.82	19.82	3.89	1.04
QCM: interest	22.24	5.79	20.10	6.49	1.52
QCM: probability of success	14.37	2.48	14.85	2.86	-.78
QCM: anxiety	12.71	4.70	14.31	6.51	-1.24

MWT-B: Mehrfachwahl-Wortschatzintelligenz-Test Version B; PANSS: Positive and Negative Syndrome Scale; QCM: Questionnaire to assess current motivation in learning situations.

subscale and total score of the O-AFP. The changes in O-AFP scores were above the cut-off, indicating reliable change. These findings are consistent with previous studies showing beneficial effects of programs including cognitive remediation and broader rehabilitation measures [5,7,8]. However, the interpretation of these findings is limited by the lack of a control group not receiving any cognitive intervention. Therefore, it is not clear whether our training interventions constitute a causal factor in these general improvements. The first

Table 2 Primary and secondary outcome measures

Variables	Plan-a-Day				Basic Cognition				ANOVA
	time: pre		post		time: pre		post		F-value interaction
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Planning and Problem-solving									
PAD "solution time"	106.89	42.36	63.38	22.46	84.80	38.05	74.24	38.92	21.95**
Planungstest "solution time"	52.19	15.95	48.92	25.02	48.63	14.41	44.67	14.65	0.03
Zoo-Map "solution time"	111.39	58.95	97.42	52.79	105.56	59.87	99.28	42.86	0.31
Functional capacity									
O-AFP "learning ability"	21.16	4.87	25.42	3.74	21.59	5.36	26.08	4.16	0.07
O-AFP "total score"	68.08	9.63	80.50	8.05	69.44	10.95	80.49	8.81	0.52

Raw scores (with standard deviation) for both groups at both time points and test statistics for the interaction time (pre/post) × group.

SD: standard deviation; O-AFP: Osnabrücker Arbeitsfähigkeitenprofil (measure of functional capacity)

**: $p < .001$; all other $p > 0.1$

Table 3 Basic cognition variables for both groups at both time points

Variables	Plan-a-Day				Basic Cognition				ANOVA
	time: pre		post		time: pre		post		F-value interaction df = 1,75
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
digit span forward "Score"	9.97	1.84	10.08	1.92	9.10	2.09	9.21	2.07	<.001
digit span backward "Score"	6.71	2.03	7.47	1.90	5.72	1.72	6.36	1.72	.13
corsi forward "Score"	8.05	2.01	8.11	2.48	8.69	1.85	9.10	1.65	.66
corsi backward "Score"	7.95	1.77	7.76	2.14	7.21	1.66	7.23	2.06	.21
LNS "Score"	10.74	2.58	11.13	2.89	10.08	2.46	10.23	2.72	.32
TMT A "time"	28.74	8.97	25.51	6.99	33.03	13.23	30.83	10.52	.26
TMT B "time"	70.18	25.16	72.34	17.51	74.21	25.15	80.03	30.79	.65
Stroop neutral "time"	797.44	141.58	785.17	138.55	842.54	193.87	767.40	177.07	8.22* (df = 1,69)
Difference incongruent-neutral "time"	76.47	98.23	58.69	86.75	74.46	97.03	48.77	81.70	.14 (df = 1,69)

Exploratory analysis of the interaction time (pre/post) × group.

SD: standard deviation; LNS: Letter-Number-Sequencing; TMT:Trail Making Test

*: $p < .01$; all other $p > 0.1$

alternative explanation to be considered is unspecific treatment effects resulting for example from hospitalization and medication. However, patients in the study were clinically stable and normally do not present short term fluctuations in performance. Another important issue is a possible effect of the intensive work therapy program on functional capacity as well as cognitive functioning. Beneficial effects of rehabilitation programs including work therapy on the OAF-P functional capacity measure have been demonstrated, although over a longer time frame [53]. Furthermore, Bell and colleagues have suggested that work therapy alone can improve cognitive functioning as it challenges memory and other cognitive functions [54]. However, to our knowledge no study has compared work therapy with a control condition in its effect on cognition.

The study's main focus was a differential effect of the training interventions on cognition and functional capacity. Regarding cognitive performance, the planning and problem-solving training lead to stronger improvement on Plan-a-Day solution time. This finding suggests that the intervention was effective at improving planning abilities. A critical objection could attribute this effect to the training of a similar task in the remediation program. However, the Plan-a-Day diagnostic and training versions differed considerably on a number of characteristics such as user interface and problem types. Therefore, although this effect might partially result from similarities between tasks, it may indicate some improvement on planning and problem-solving. There were no differential effects on the other planning tests, which address this construct on a less complex level. This difference in complexity might explain the difference in effects. In the training program, participants learn to deal with planning demands typical for real-world environments, for example involving goal conflicts requiring to skip one element. These are strategies, which are unlikely to be helpful in tasks like the Tower of London, which always have a complete and unequivocal solution.

In addition, we found a significant main effect of time for Plan-a-Day and Planungstest, suggesting that participants in both groups improved in planning ability. A critical objection would attribute this finding to a task repetition effect, although different versions of the tests were employed at both measurement points [55]. Alternatively, both the training of a more complex planning task and a set of less complex basic cognition tasks might lead to a similar improvement through different mechanisms. Overall, our results suggest that some deficits in planning and problem-solving of patients suffering from schizophrenia can be improved by a cognitive training program within three weeks. The advantage of a specific training of these functions was limited to the outcome measure most closely related to the training program. However, the improvement of the planning and problem-solving group specifically on the task most closely approaching real-world requirements suggests a potential for successful generalization to functional outcomes.

In an exploratory analysis, we addressed the issue of change in basic cognitive functions. A significant time × group interaction was only observed for reaction time in the neutral condition of the Stroop task, suggesting an advantage for basic cognition training. This result has to be viewed with caution, because we did not correct for multiple comparisons due to the exploratory character of this analysis. Reaction time in the neutral condition is a relatively pure measure of processing speed, which was also trained in the basic cognition training group.

This suggests some degree of generalization across measures of processing speed, but not to other cognitive measures.

An important finding of the study is the absence of a significant differential effect of the two training programs on functional capacity. This result was observed despite the fact that the planning and problem-solving group had more contact with the trainer and explicitly practiced transfer to daily activities. Although there is meta-analytic evidence for an effect of cognitive remediation on functional outcome or respective proxy measures, this issue still remains controversial in the light of well-conducted studies with negative results [4,15]. Thus, one way to explain the absence of a differential effect would be that none of the two interventions had an effect on functional capacity.

However, Medalia et al. observed significant improvements on the Independent Living Scale specifically for the problem-solving intervention [28]. It has to be noted that our sample size was about twice as large in each treatment group and should have resulted in greater power to detect significant differences. Therefore, other differences between the studies need to be considered to explain the discrepant findings. First of all, it is important to consider similarities and differences between our intervention and the one employed by Medalia and colleagues. While both studies addressed problem-solving, our study explicitly focused on planning as a key cognitive function. In the Medalia study, planning was clearly involved in the problem-solving intervention, but a broader set of cognitive functions was likely required, although not explicitly specified. An important issue in the classification of cognitive remediation techniques is the amount of strategy teaching involved [56]. In both studies, participants in the problem-solving group were actively supported in the use of efficient problem-solving strategies. In contrast, strategies for compensating existing cognitive deficits were not explicitly trained in either study. Thus, both problem-solving interventions fill the middle ground on a continuum from drill-and-practice to compensatory approaches. Lastly, Medalia and colleagues place a strong emphasis on promoting intrinsic motivation through an engaging task environment and personal feedback. Although this was not the major theoretical background for the development of Plan-a-Day, similar elements can be found in our training task. However, in our study patients trained in small groups instead of individual training, which might have led to less individualized support and feedback. Task motivation did not differ between the two interventions, which in turn might have contributed to the observed lack of differences.

In addition, a number of factors relating to the setting and the intervention have to be considered. First, in contrast to the chronic inpatient sample in the Medalia et al. study, we included patients who were living in the community before elective admission for a treatment program promoting return to work. In addition, most patients had a relatively short duration of illness with mild impairment in cognitive functioning. A tentative interpretation of both studies would suggest that more severely impaired patients benefit more from problem-solving training in comparison to other trainings, while higher-functioning patients do not show this differential effect. Second, the duration and overall exposure to the intervention might have been too limited to produce differences between treatment groups on functional capacity. Our study was shorter than most studies of cognitive remediation (e.g. [5,6,57]), but the overall treatment exposure was larger than in the problem-solving study by Medalia et al. Nevertheless, the transfer to functional capacity in a work therapy setting might require a longer time frame. Second, in contrast to the study by Medalia, our patients participated in a broader rehabilitation program including intensive work therapy. In this enriched environment, the specific effect of a differential cognitive intervention might be more difficult to detect. Bell and colleagues have suggested that under these circumstances, a differential effect might only emerge after other treatments and supports are withdrawn [54]. Third, the control conditions differed between the two studies. In our study, the control group trained on a set of three different functions, which might have increased the effects of the basic cognition training. This combination of training targets is now implemented in most remediation programs and might be advantageous for generalization to functional outcome.

Overall, the effects of the interventions on a cognitive level were limited to measures that are relatively close but not identical to the training procedure. Whether these effects are larger and more generalized when patients receive cognitive remediation over longer time frames and in other settings remains an open issue. The lack of a differential effect on functional capacity might also result in part from the fact that both planning and processing speed have been shown to be related to functional outcome [58]. Thus, even though the interventions may affect different cognitive functions to some extent, there might be no differential effect on functional capacity. The original hypotheses that training higher levels of cognitive functioning (planning and problem-solving) provides in itself a benefit over training of basic cognition could not be confirmed.

Conclusion

Improvements in cognitive functioning and functional capacity were observed after training of planning and

problem-solving as well as basic cognition. However, no differential effect of targeting specific cognitive functions on functional capacity could be established. Small differences on cognitive outcome variables indicate a potential for differential effects. This will have to be addressed in further research including longer treatment programs and other settings. However, at present there is no conclusive evidence that training cognitive functions on different levels leads to differential improvement in patient-relevant outcome measures.

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Authors' contributions
SK, DR and MW designed the study and wrote the protocol. DH and JF developed the Plan-a-Day training and diagnostic versions. KR and MR collected the data. KR, DH and MB undertook the statistical analyses and prepared them for presentation. KR and SK wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Competing interests
JF has received royalties from Hasomed GmbH, Germany. DH and JF receive royalties for the Plan-a-Day training program from Schuhfried GmbH, Austria. All other authors declare that there are no potential conflicts of interest.

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