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ORIGINAL PAPER

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Associations of SNAP-25 polymorphisms with cognitive dysfunctions in Caucasian patients with schizophrenia during a brief trail of treatment with atypical antipsychotics

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Abstract The synaptosomal-associated protein of 25 kDa (SNAP-25) is part of the soluble *N*-ethylmaleimide-sensitive fusion protein (NSF) attachment receptor (SNARE), which mediates synaptic neurotransmission. In earlier studies a possible involvement of this protein in schizophrenia has been shown. As neurocognitive impairment is a core feature in the pathology of schizophrenia and considered to be a putative endophenotype according to genetic studies we investigated the influences of different SNAP-25 polymorphisms on neuropsychological test results before and during treatment with atypical antipsychotics. A total of 104 schizophrenic patients treated with atypical antipsychotics were genotyped for three different polymorphisms of the SNAP-25 gene (*Mnl*I, *Tai*I and *Dde*I in the 3′-UTR). Cognitive function was assessed at baseline, week 4 or 6 and week 8 or 12. Results of individual neuropsychological tests were assigned to six cognitive domains (reaction time and quality; executive function; working, verbal and visual memory) and a general cognitive index. The *Mnl*I and *Tai*I polymorphisms showed no associations to deficits on neuropsychological test results. In contrast, we observed a significant relation between the *Dde*I polymorphism of the SNAP-25 gene and cognitive dysfunctions. Homozygote T/T allele carriers of the *Dde*I polymorphism showed significant better neuropsychological test results in cognitive domains verbal memory and executive functions than those with the combined T/C and C/C genotypes ($P < 0.01$) at all three time points, but no differences in response to treatment with atypical antipsychotics. Additionally, TT carriers exhibited significantly better results in a general cognitive index ($P < 0.05$). As we observed an association between the *Dde*I polymorphism of the SNAP-25 gene and cognitive dysfunctions of schizophrenic patients our finding suggests that the SNAP-25 gene could play a role in the pathophysiology of neurocognitive dysfunctions in schizophrenia but is not predictive for treatment response with atypical antipsychotics.

Key words SNAP-25 · schizophrenia · atypical antipsychotics · executive function · cognitive improvement

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Introduction

The synaptosomal-associated protein of 25 kDa (SNAP-25) plays an integral role in vesical docking and fusion machinery mediating the release of neurotransmitters from the presynaptic membrane into the synaptic cleft. Together with other proteins including the synaptic vesicle protein VAMP (vesicle-associated membrane protein, also called synaptobrevin) or the plasma membrane protein syntaxin (also HPC-1), it forms the so-called SNARE (soluble *N*-ethylmaleimide-sensitive factor attachment receptor) protein complex [2]. SNAP-25 is widely but differentially expressed by diverse neuronal subpopulations of the adult brain. Moreover, its transient localization in axons within the developing brain indicates that SNAP-25 might be required for plasticity of neuro- and synaptogenesis [46, 59].

The SNAP-25 protein was considered to be associated with attention-deficit-hyperactivity disorder, since the coloboma mouse heterozygous for the

deletion of the SNAP-25 gene displayed spontaneous hyperactivity responsive to dextroamphetamine [23, 24]. Consistent with these results, an association of two SNAP-25 polymorphisms (M*nl*I and D*de*I) of the 3́UTR region with ADHD was described in genetic studies [4, 7, 34]. Although the resulting heterozygous and semi-dominant mutation in the coloboma mouse model seems not to inhibit neurotransmission totally, it could considerably alter vesicle release. As there is strong evidence that dysregulations in neurotransmitter release, as in the dopaminergic pathway or the NMDA receptor-mediated glutamate transmission, play important roles in the pathogenesis of schizophrenia [20, 26, 43, 49], a pathophysiological involvement of SNAP-25 should be considered.

Neurocognitive impairment has been viewed as a key factor in schizophrenia pathology. A century ago, Kraepelin and Bleuler were among the first clinicians to include impaired cognitive processes as core features in their descriptions of schizophrenia [6, 33]. Over the past decades, a wealth of new empiric evidence associating specific cognitive impairments with schizophrenia has accumulated [36], with current estimates suggesting that two-thirds of patients with schizophrenia have impaired cognition [47] with the remaining "cognitively normal" patients likely to experience a decline in their cognitive function prior to onset of their illness. It could be demonstrated in high-risk-studies of unaffected relatives of schizophrenic patients compared to healthy controls that they also suffered from latent cognitive dysfunctions becoming evident in early childhood [12, 45]. Cognitive deficits, which lead to subtle early premorbid impairments, may be present prior to the first clear-cut psychotic episode and seem to remain stable at least over the early course of schizophrenia [1, 15]. Moreover, these deficits have been observed to remain stable in ambulatory patients with schizophrenia regardless of changes in clinical state [22]. Due to its considerable trait stability neurocognitive symptoms have received growing attention in genetic studies as a putative endophenotype [8].

Until now several well-established candidate genes for schizophrenia have been associated with neurocognitive dysfunctions [9, 11, 14, 56].

Neurocognitive dysfunctions are considered to be more inaccessible towards psychopharmacological interventions than other more fluctuating positive or even negative symptoms [36].

However, a meta analysis regarding cognitive factors in the treatment of schizophrenia summarized as a broad consensus that atypical antipsychotics can improve neurocognitve deficits, both in patients considered to be resistent to other psychopharmacological interventions and in previously untreated patients [37]. This is consistent with recent publications in the field demonstrating that atypical antipsychotics exhibited considerable positive effects on cognitive dysfunctions [30, 31, 40, 50, 53, 54]. Interestingly, degree and quality of these effects were quite different and might represent the heterogeneity of receptor profiles among atypical antipsychotics.

Although little is known about potential effects of SNAP-25 on cognitive symptoms in schizophrenia, there are recent hints for an association of the SNAP-25 gene with cognitive abilities according to a family-based study in two independent Dutch cohorts [16]. In this study two single-nucleotide polymorphisms (rs363039 and rs363050) out of twelve investigated in the SNAP-25 gene showed a significant relation to standardized intelligence measures conducted in all individuals.

In order to investigate whether SNAP-25 could have an influence on neurocognitive functions of schizophrenic patients before or during treatment with atypical antipsychotics, we compared the neuropsychological test results of patients with three different SNAP-25 polymorphisms (M*nl*I, T*ai*I and D*de*I in the 3′-UTR).

Methods

Patients

Outpatients and hospitalised patients aged 18–65 years were eligible to participate in the study. Patients were participants of different randomized, double-blind parallel-group designed or open-label studies and were assigned to monotherapy with an antipsychotic for a minimum of 8 and a maximum of 12 weeks. In total, the data of 104 schizophrenic patients (64 males and 40 females, mean age 33.36 SD (11.55) years, mean age of onset 27.30 SD (9.20) years, mean duration of illness 5.96 SD (7.88) years) were retrospectively analyzed in this study. All patients were of Caucasian origin, 88% were of German descent, 4% of the Turkish and 8% of the Slavic population.

Patients were diagnosed according to DSM-IV criteria as either paranoid (n = 67) or disorganised schizophrenia (n = 16), followed by schizoaffective disorder (n = 13), psychotic disorder not otherwise specified (n = 5) and schizophrenia of catatonic (n = 1), residual (n = 1) or undifferentiated type (n = 1). For diagnostic assessments the Structured Clinical Interview for DSM-IV Axis 1 Disorders (SCID-I) was administered. Diagnosis was established through clinical judgement of two independent psychiatrists.

Exclusion criteria consisted of substance abuse, suicidal tendencies, laboratory or ECG/EEG abnormalities, pregnancy or lactation and significant medical history (brain surgery, dementia, unstable somatic conditions, viral infections). The study was approved by the ethics committee of the medical faculty of the University of Munich. All patients gave written informed consent prior to study inclusion. This study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

Treatment

Fifty-two percent (n = 54) of the patients were previously treated with different oral antipsychotic drugs, however, with insufficient efficacy or intolerable side effects. Of these 22 patients were treated with conventional antipsychotics and 32 patients were treated with atypical antipsychotics. One patient received mirtazapine (wash-out period of 14 days) and another citalopram (wash-out period of 2 days) prior to inclusion.

Table 1 Neurocognitive tests used to assess the six cognitive domains

Domain assessed	Test name	Variable measured
Working memory	Rey auditory verbal learning, list 1 and 2, trial 1 (RAVLT) [52]	Working memory function
	Letter-number span sequencing task [13]	Auditory working memory
	Self ordered pointing task (SOPT) [18]	Visual working memory
Verbal memory	Rey auditory verbal learning test (RAVLT), list 1, trials 1–5, 6–8	Verbal declarative memory function
Reaction time and quality	Neurobat S—short version [68] trails A test [51]	Sustained attention and sensomotor flexibility tests
Executive functions	Trails B test	General psychomotor function
	Verbal fluency and category fluency [60]	Category and letter fluency measures
Visual memory	Wechsler memory scale-revised [21]	Memory of non-verbal stimuli
	One point test [28]	Visuospatial working memory

No patient was previously treated with a depot antipsychotic formulation. Pre-treated patients passed a washout period of 2–14 days before entering treatment with an atypical antipsychotic. The mean wash-out time was 9.7 SD (28.4) days. Forty-eight percent (n = 50) of the patients were either drug naive or drug free for a minimum of 3 months before entering the study.

During the study phase patients were treated with different second generation antipsychotics (in an unequal distribution, the majority with quetiapine (n = 31; mean dose = 586.86 SD (169.12) mg), followed by risperidone (n = 26; mean dose = 4.93 SD (0.87) mg), aripiprazole (n = 26; mean dose = 14.97 SD (4.60) mg) and olanzapine (n = 21; mean dose = 15.82 SD (5.44) mg) over a period of 8–12 weeks. In all studies the initial phase of treatment pursued a fixed-dose titration period of 7 days for each atypical antipsychotic according to the recommended guidelines of the manufacturer and adapted to the specific design of the individual study. During the following flexible dose treatment phase dosage was adjusted according to the instructions of the individual investigator within a certain defined range for each different antipsychotic. In the event that a study participant did not respond effectively to the maximum dose, the patient was withdrawn from the study. Throughout the study, lorazepam (≤4 mg/day) and zopiclone (≤15 mg/day) were allowed for agitation and insomnia. Biperidene hydrochloride (≤8 mg/day) was used to treat extrapyramidal symptoms (EPS). Mean daily doses of theses substances did not differ significantly between genotype groups throughout the study.

Moreover, lorazepam and zopiclone had to be discontinued at least 24 h prior to neurocognitive testing to assure an unaffected neuropsychological test result.

Comprehensive medical assessments (vital signs, ECG, EEG, laboratory tests) were carried out on a regular basis.

Neurocognitive test battery

The neurocognitive tests were chosen to represent a range of reliable and validated tests, which have been used in similar trials [53, 54, 58, 61, 65, 66, 70]. The entire battery (Table 1) took between 90 and 120 min to complete. With the exception of Neurobat-S short version, the One-point test, and Self-ordered-pointing task (SOPT), we used three different parallel versions of the neurocognitive tests at the three test sessions. The individual neurocognitive tests were transformed into z-scores and grouped into six cognitive domains: reaction time, reaction quality/attention, executive functions, working memory, verbal learning and memory, and visual memory. In addition, a global cognitive index was constructed by summing and averaging across the z-scored variables of neurocognitive tests.

The neurocognitive test battery was administered at three time points, prior to study inclusion, following 4 or 6 and 8 or 12 weeks of treatment, depending on the study design the patient participated. During the initial assessment, premorbid intelligence was ascertained using the Multiple Choice Word Test-B (MWT-B) [35]. Results from this vocabulary test correlate with "crystallised intelligence", which remains stable during adulthood and is relatively independent of concurrent psychopathology.

Genotyping

Genomic DNA was isolated from whole blood according to standard procedures. Three restriction fragment length polymorphisms (RFLP) in the SNAP-25 were genotyped with the enzymes *Mnl*I, *Dde*I and *Tai*I (MBI Fermentas, Amherst, NY, USA). The M*nl*I- (T/G substitution) and the *Dde*I- (T/C substitution) SNPs are closely opposed (four basepairs apart) and can be visualized using the same PCR amplicon. The T*ai*I RFLP is a T/C substitution 658 and 654 bp downstream of the M*nl*I and D*de*I polymorphisms. The corresponding SNP ID numbers were as follows: rs3746544 (M*nl*I); rs1051312 (D*de*I), rs8636 (T*ai*I) from http://www.ncbi.nlm.nih.gov/SNP/.

The M*nl*I/D*de*I primer sequences were: forward: 5′-TTC TCC TCC AAA TGC TGT CG-3′; reverse: 5′-CCA CCG AGG AGA GAA AAT G-3′. The PCR reaction consisted of 50 ng DNA, 0.6 µl 10× PCR puffer, 200 µM of each dNTP, 0.6 µM of each primer and 0.2 µl Taq (Amplitaq Gold, Applied Biosystems, Foster City, USA) in a final volume of 20 µl. After denaturation at 95°C for 5 min, 35 cycles of PCR were performed with the following conditions: 94°C for 30 s, 60°C for 40 s, 72°C for 30 s and a final extension at 72°C for 7 min. M*nl*I and D*de*I digestion was done by adding 2 µl 10× digestion puffer, 0.25 µl of M*nl*I (2.5 U), respectively D*de*I (2.5 U) to 10 µl of the PCR product in a final volume of 15 µl. After digestion at 37°C overnight for M*nl*I and D*de*I the samples were run on a 3% agarose gel. The uncut allele (T) of the M*nl*I RFLP appeared as a 261 bp band, while the cut allele (G) had bands at 210, 46 and 5 bp. For the D*de*I polymorphisms the uncut allele (T) was represented by a 261 band and the cut allele (C) by bands at 228 and 33 bp.

For the T*ai*I RFLP the following primers were applied: forward: 5′-TGG AAA TTA TGT CAA ATG G-3′; reverse: 5′-AAC AAA CCA CAG GGG AAA TG-3′. The PCR reaction used the following mixture: 50 ng DNA, 1.5 µl 10× PCR puffer, 200 µM each dNTP, 0.6 µM of each primer and 0.15 µl Taq (Amplitaq Gold, Applied Biosystems, Foster City, USA) in a final volume of 15 µl. PCR conditions were the same as for the M*nl*I/D*de*I polymorphisms. PCR product of 15 µl were digested by adding 2 µl 10× digestion puffer, 0.2 µl T*ai*I (2U) and 2.8 µl deionized H_2O at 65°C overnight. The polymorphism was visualized on a 2.5% agarose gel, yielding an uncut band (T) at 150 bp and bands of 90 and 60 bp for the cut allele (C).

Data analysis

Data analyses were carried out using SPSS (version 14.0 for windows) software. Data were analysed using an univariate analysis of covariance (ANCOVA) controlling for differences in neurocognitive functioning between patient's genotypes. As pre- and untreated patients were included into the study and patients were treated with different atypical antipsychotics, differences between genotype groups were analysed by using these possible confounders as covariates in the variance analyses. Moreover, the variance analyses were corrected for age, age of onset, the MWT-B, as a measure of premorbid intelligence, and re-testing by including these variables

as covariates in the calculations. Paired *t* tests were performed for the analysis of changes in cognitive test results within the same genotype group from baseline to endpoint. Pearson's χ^2 test was used to test for nominal variables like the distribution of different atypical antipsychotics and the number of previously pre- or untreated patients between genotype groups. Differences in demographic variables like age, age of onset and duration of illness between genotype groups and differences between pre- and untreated patients were analysed by using the Student's *t* test for independent samples. Lacking neurocognitive data of patients due to an earlier termination of the study were approximately evaluated by using the Last-observation-carried-forward (LOCF) procedure. To minimize the type I error we performed the Bonferroni correction.

The calculation of linkage disequilibrium (LD) between the *Tai*I and *Mnl*I polymorphisms was performed with the computer program COCAPHASE 2.35 (http://www.hgmp.mrc.ac.uk) [10]. We used D′ to describe the magnitude of LD.

Results

Genotypes

We genotyped for the three polymorphism in the 3′-UTR region in the SNAP-25 gene (*Tai*I T/C, *Dde*I T/C, *Mnl*I T/G).

Due to the relatively low frequencies of the C allele of the D*de*I polymorphism (TT = 56.6%, TC = 38.7%, CC = 4.7%), the G allele of the M*nl*I polymorphism (TT = 40.0%, TG = 51.4%, GG = 8.6%) and the T allele of the T*ai*I polymorphism (TT = 8.5%, TC = 51.7%, CC = 39.8%) we combined the heterozygote and homozygote carriers of these alleles for a better statistical analysis of different genotype characteristics. Genotype groups of all three polymorphisms did not differ significantly according to demographic characteristics like age ($F = 0.188$, $T = -0.576$, $P = 0.566$), age of onset ($F = 0.452$, $T = -0.412$, $P = 0.681$) or duration of illness ($F = 0.193$, $T = -0.096$, $P = 0.924$). There were neither significant differences in distribution of previously untreated versus pre-treated patients ($\chi^2 = 0.897$, $df = 1$, $P = 0.344$) nor in distribution of different atypical antipsychotics ($\chi^2 = 3.137$, $df = 3$, $P = 0.371$) between genotype groups of all three investigated polymorphisms.

We further found that the SNAP-25 *Tai*I and *Mnl*I polymorphisms are in linkage disequilibrium ($D' = 0.99$) in our study sample. The *Ddel*I polymorphism was not in linkage disequilibrium to the two other polymorphisms.

Cognitive functioning

We observed an improvement in all neurocognitive domains from baseline to the endpoint of observation reaching significance in working ($T = -5.95$, $P < 0.001$), verbal ($T = -4.21$, $P < 0.001$) and visual memory ($T = -4{,}10$, $P < 0.001$) as well as in reaction time ($T = -2.25$, $P = 0.027$), reaction quality/attention ($T = -3.12$, $P < 0.002$) and a general cognitive index ($T = -6.61$, $P < 0.001$) in all patients. Homozygote T allele carriers of the SNAP-25 D*de*I polymorphism had a higher score (26.12 SD (7.69)) in the MWT-B test than patients in the combined TC/CC genotype group (22.89 SD (9.37)) without reaching statistical significance ($F = 1.97$, $P = 0.145$). The scores from the individual neurocognitive tests are shown in Table 2. TT allele carriers of the D*de*I SNAP-25 polymorphism performed significantly better in nine individual neurocognitive tests than patients in the combined group of heterozygote and homozygote C allele carriers at different time points (Table 2).

Differences in individual tests are reflected in results of neurocognitive domains and a general cognitive index (Figs. 1, 2). In working memory TT allele carriers gained significantly better test results at baseline (z-scores: −0.15 SD (0.57)) than patients in the combined TC/CC genotype group (−0.41 SD (0.69); $F = 4.36$, $P = 0.039$), but this result lost statistical significance after correcting for multiple testing (Bonferroni correction). In verbal memory (mean z-scores TT vs. TC/CC: 0.07 SD (0.79) vs. −0.47 SD (1.04); $F = 5.7$, $P = 0.004$) and executive functions a statistically significant superiority of TT allele carriers in test results was observed at all three test sessions while most distinctive superior results were observed in executive functions (mean z-scores TT vs. TC/CC: 0.09 SD (0.35) vs. −0.20 SD (0.46); $F = 7.1$, $P = 0.001$). Additionally, averaging of results in neuropsychological tests resulted in significant higher z-scores in general cognitive indices at all three time points in homozygote T allele carriers than in heterozygote or homozygote C allele carriers. After correction for multiple testing this result remains only statistical significant at the second time of neuropsychological testing (week 4 or 6; mean z-scores TT vs. TC/CC: 0.06 SD (0.47) vs. −0.22 SD (0.66); $F = 3.7$, $P = 0.029$), but also for a mean score averaged over all three test sessions (Fig. 2; mean z-scores TT vs. TC/CC: 0.02 SD (0.47) vs. −0.26 SD (0.64); $F = 3.6$, $P = 0.031$). Regarding genotype differences in response to antipsychotic treatment there were no significant between-group results, but the numerical improvement of TT allele carriers in working (mean improvement of z-scores TT vs. TC/CC: 0.29 SD (0.42) vs. 0.27 SD (0.54); $F = 0.54$, $P = 0.58$), verbal (0.35 SD (0.61) vs. 0.23 SD (0.87); $F = 0.44$, $P = 0.65$) and visual memory (0.30 SD (0.52) vs. 0.16 SD (0.60); $F = 0.79$, $P = 0.46$) was more pronounced than in the TC and CC genotype group, while TC and CC allele carriers gained slightly better results in reaction time (mean improvement of z-scores TT vs. TC/CC: 0.11SD (0.48) vs. 0.13 SD (0.63); $F = 0.029$, $P = 0.97$), reaction quality/attention (0.22 SD (0.91) vs. 0.43 SD (1.06); $F = 1.18$, $P = 0.31$) and executive functions (0.04 SD (0.32) vs. 0.06 SD (0.46); $F = 0.75$, $P = 0.47$) up to week 8 or 12.

Table 2 Individual neuropsychological tests at baseline, week 4 or 6 and week 8 or 12

Category	SNAP-25 DdeI (TT) (n = 58)			SNAP-25 DdeI (TC/CC) (n = 46)			Between-difference[a]					
	Baseline	Week 4 or 6	Week 8 or 12	Baseline	Week 4 or 6	Week 8 or 12	Baseline		Week 4 or 6		Week 8 or 12	
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	*F*	*P*	*F*	*P*	*F*	*P*
Working memory												
Auditory verbal learning test												
List 1, trial 1, correct responses	5.07 (1.52)	6.10 (2.16)	6.93 (2.63)	5.13 (1.64)	6.11 (2.13)	6.78 (2.72)	0.12	0.88	0.34	0.71	1.01	0.37
List 2, trial 2, correct responses	5.56 (1.94)	5.40 (1.97)	5.40 (2.03)	4.78 (2.11)	4.73 (2.35)	5.07 (2.68)	1.53	0.22	1.03	0.36	0.32	0.73
Letter-number span	13.74 (3.62)	14.13 (3.60)	14.57 (3.68)	11.04 (4.53)	11.49 (4.79)	11.86 (4.78)	5.71	**0.005**	6.81	**0.002**	7.12	**0.001**
Self-ordered pointing tasks 1–4, errors	7.12 (4.88)	5.98 (5.15)	5.91 (5.30)	8.50 (4.96)	7.14 (5.41)	7.29 (5.61)	0.4	0.67	0.67	0.52	0.59	0.56
Verbal memory												
Auditory verbal learning test												
List 1, trials 1–5 (learning trials), correct responses	43.20 (12.36)	45.83 (12.58)	47.95 (13.92)	39.74 (12.70)	43.78 (12.99)	45.61 (13.66)	0.98	0.38	0.39	0.68	0.81	0.45
List 1, trial 6 (interference recall), correct responses	8.51 (3.37)	9.62 (3.80)	9.71 (3.86)	7.27 (3.61)	8.38 (3.37)	8.47 (3.35)	1.7	0.19	1.73	0.18	1.64	0.2
List 1, trial 7 (delayed recall), correct responses	7.88 (3.32)	9.02 (3.78)	9.54 (3.85)	6.64 (3.84)	7.78 (3.77)	7.86 (3.76)	1.24	0.3	1.98	0.15	2.58	0.08
Recognition Form, correct recognitions	12.09 (2.91)	12.07 (2.74)	12.23 (2.80)	10.84 (3.27)	10.73 (3.47)	11.42 (3.23)	3.53	**0.03**	4.48	**0.01**	3	0.06
Recognition Form, correct rejections	33.98 (1.29)	34.46 (0.76)	34.50 (0.83)	33.24 (2.25)	33.13 (2.46)	33.26 (3.08)	2.9	0.06	8.61	**<0.001**	5.22	**0.01**
Reaction time												
Sensomotoric 1–4 (ms)	513.90 (85.93)	500.71 (74.70)	499.07 (72.55)	547.52 (104.50)	535.84 (99.85)	538.98 (102.55)	2.03	0.14	3	0.06	4.35	**0.02**
Duration of attention 1–3 (ms)	435.08 (44.39)	435.70 (58.15)	437.89 (56.96)	471.27 (216.87)	431.25 (58.34)	430.34 (54.68)	0.22	0.81	0.05	0.95	0.07	0.93
Trail making test A (s)	35.39 (14.17)	31.09 (11.91)	30.79 (11.76)	51.38 (41.19)	42.13 (27.09)	40.30 (26.98)	3.76	**0.03**	3.3	**0.04**	2.65	0.08
Reaction quality/attention												
Sensomotoric trial 1–4												
Errors	2.34 (3.32)	1.69 (1.91)	1.84 (2.23)	3.01 (4.73)	1.90 (3.06)	1.28 (1.78)	1.61	0.21	0.46	0.63	0.69	0.51
Correct responses	21.91 (3.68)	23.76 (7.27)	22.70 (2.61)	20.27 (6.03)	21.95 (4.42)	22.69 (3.72)	1.03	0.36	0.47	0.63	0.42	0.66
Duration of attention trial 1–3												
Errors	9.85 (11.57)	8.68 (8.26)	8.04 (8.23)	9.27 (8.10)	7.84 (9.28)	7.24 (8.86)	0.84	0.43	0.65	0.52	0.77	0.47
Correct responses	229.23 (15.28)	231.13 (12.68)	232.18 (12.54)	229.02 (12.67)	232.87 (11.45)	233.30 (10.71)	0.82	0.44	0.88	0.42	0.57	0.57
Executive functions												
Verbal fluency, number of acceptable words	44.35 (14.09)	44.45 (15.98)	44.00 (15.72)	36.78 (17.41)	38.13 (16.95)	39.93 (18.31)	2.14	0.12	1.72	0.19	0.91	0.41
Category fluency, number of acceptable words	35.37 (9.18)	34.98 (8.78)	35.23 (8.49)	31.49 (11.48)	31.27 (9.24)	33.09 (10.21)	1.35	0.26	2.49	**0.09**	0.95	0.39
Category fluency, number of repetitions	0.21 (0.41)	0.39 (0.97)	0.41 (0.71)	0.47 (0.84)	0.58 (1.03)	0.43 (0.79)	3.72	**0.03**	1.08	0.35	0.15	0.86
Trail making test B (sec)	83.68 (48.21)	71.75 (36.60)	69.45 (36.79)	120.91 (85.13)	110.71 (72.87)	100.36 (65.93)	3.25	**0.04**	6.12	**0.003**	4.38	**0.02**
Visual memory												
Wechsler visual memory scale												
Immediate reproduction	31.96 (5.23)	33.42 (4.99)	33.50 (4.64)	28.98 (9.20)	31.37 (7.60)	31.14 (7.60)	2	0.14	1.97	0.15	2.24	0.11
Delayed reproduction	26.28 (8.58)	29.82 (8.81)	30.11 (8.56)	22.77 (12.06)	25.95 (11.03)	26.77 (11.17)	0.94	0.4	2.23	0.11	2.3	0.11
One point test												
Immediate reproduction	13.65 (4.22)	13.70 (4.14)	13.06 (3.66)	12.94 (3.38)	13.53 (6.33)	12.99 (6.28)	0.21	0.81	0.002	1.998	0.2	0.82
Delayed reproduction	19.71 (8.67)	17.74 (5.41)	17.53 (5.41)	19.31 (11.00)	18.91 (8.79)	19.41 (9.95)	1.78	0.18	3.1	0.05	6.05	**0.004**

[a]Between genotype group difference TT versus TC/CC allele carriers at baseline, week 4 or 6 and week 8 or 12

Bold type indicates a significant advantage of TT versus TC/CC allele carriers ($P < 0.05$). The different trial numbers listed above indicate the versions of the tests used in this study

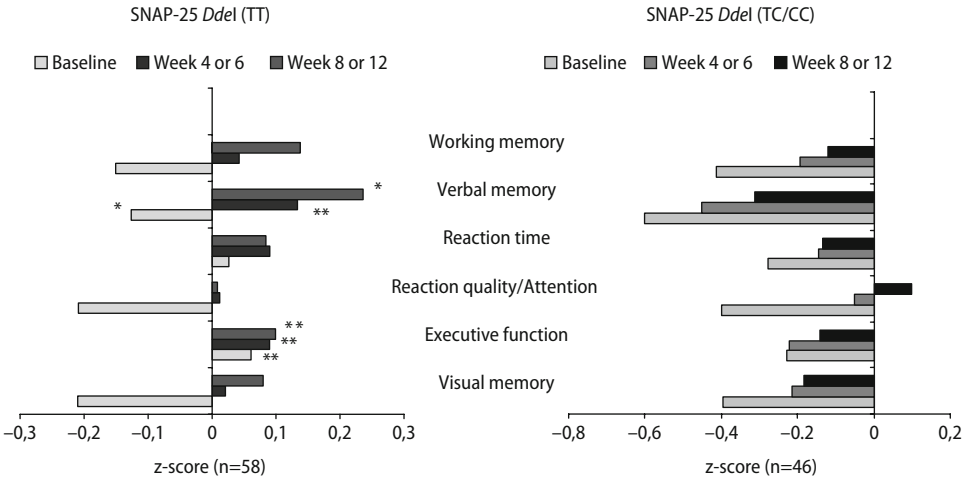
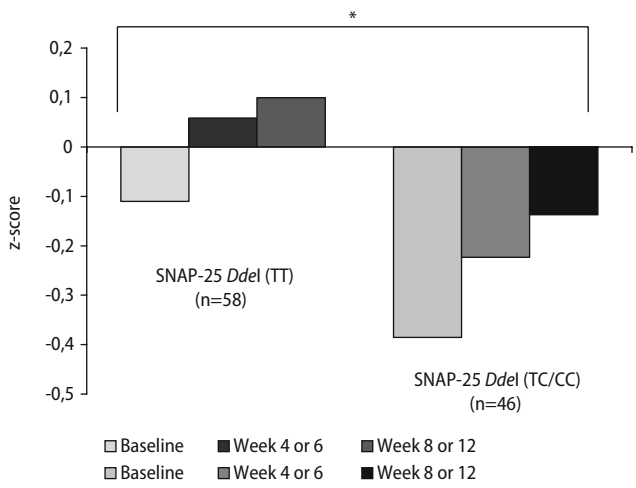


Fig. 1 Mean z-scores of six neurocognitive domains at baseline, week 4 or 6 and week 8 or 12

* p<0.05, ** p<0.01; TT vs. TC/CC allele carrier

Compared to the significant results regarding the D*de*I polymorphism of the SNAP-25 gene there were no significant differences in neuropsychological test results according to the investigated genotype groups of the *Mnl*I and *Tai*I SNAP-25 polymorphisms.

Previously untreated patients had significantly better neuropsychological test results compared with pre-treated patients in working memory at baseline (−0.07 SD (0.55) vs. −0.42 SD (0.63); $T = -2.77$, $P = 0.007$), at week 4 or 6 (0.13 SD (0.70) vs. −0.20 SD (0.76); $T = -2.14$, $P = 0.036$) and in executive functions at baseline (0.10 SD (0.35) vs. −0.15 SD (0.52); $T = -2.62$, $P = 0.01$). Numerical differences continued throughout the study phase, but lost its statistical significance. However, pre-treated patients were significantly older (36.28 SD (11.46) vs. 29.49 SD (10.17) years; $T = 2.96$, $P = 0.004$), characterized by a longer duration of illness (6.96 SD (8.78) vs. 3.74 SD (5.10) years; $T = 2.08$, $P = 0.040$) with more hospitalizations (3.40 SD (3.05) vs. 1.59 SD (1.32); $T = 3.54$, $P = 0.001$) as well as a lower MWT-B score (23.45 SD (9.53) vs. 27.19 SD (7.17); $T = -2.09$, $P = 0.04$) than untreated patients indicating an unfavourable course of disease in these patients.



* p<0.05, TT vs. TC/CC allele carrier

Fig. 2 Mean global cognitive indices at baseline, week 4 or 6 and week 8 or 12

Discussion

In this study we found that schizophrenic patients improved in test results of several neurocognitive domains during 8–12 weeks of treatment with different atypical antipsychotics (see Table 2, Fig. 1). Although the degree of the observed neurocognitive improvement did not vary significantly between the investigated SNAP-25 genotype groups over time, TT allele carriers of the D*de*I polymorphism exhibited significantly better results in several individual neuropsychological tests, in neurocognitive domains verbal memory and executive functions as well as in a general cognitive index than a group of combined heterozygote and homozygote C allele carriers at baseline and at two further time points during a treatment with atypical antipsychotics (see Figs. 1, 2).

There were no significant associations between M*nl*I and T*ai*I polymorphisms of the SNAP-25 gene and cognitive functions neither at all three neuropsychological test sessions nor in the degree of improvement of neurocognitive symptoms throughout the antipsychotic treatment phase in our study. Nevertheless, we found that the SNAP-25 *Tai*I and *Mnl*I polymorphisms are in linkage disequilibrium ($D' = 0.99$) in our study sample, a finding which is also formerly described by Mueller et al. [42]. The *Dde*lI polymorphism was not in linkage disequilibrium to the two other polymorphisms possibly suggesting that a putative recombination hotspot might lie between these SNP's.

The finding of an improvement in different cognitive domains during a treatment with atypical an-

tipsychotics is consistent with the literature [37, 48, 53, 54].

Concerning a possible underlying mechanism of the SNAP-25 gene and cognitive symptoms in schizophrenia only speculative arguments or data from literature can be presented here.

Actually, there are several studies associating SNAP-25 with schizophrenia indicating alterations in SNAP-25 levels in different brain areas or CSF of schizophrenic patients versus healthy controls [19, 25, 27, 41, 62, 63]. However, the influence of antipsychotic treatment on SNAP-25 levels remains controversial. Even though there are several earlier studies lacking to identify an impact of antipsychotics on SNAP-25 distribution [44, 57], others found either a decrease or an increase of SNAP-25 during a treatment with haloperidol or chlorpromazine depending on the brain region investigated in rats [3, 69]. This led some authors to the conclusion that the alterations of SNAP-25 protein levels may be more important with respect to antipsychotic drug response than in the etiology of schizophrenia [42, 69]. However, significant differences in neurocognitive functions between SNAP-25 D*de*I genotypes observed in our study were not significantly associated with an antipsychotic drug effect, but constituted a rather robust characteristic trait from the beginning and throughout the course of the study. While a possible relationship between SNAP-25 and antipsychotic treatment remains to be elucidated in future studies, our result indicates a possible association of the SNAP-25 gene with the degree of cognitive dysfunctions and could therefore strike etiological aspects of schizophrenia.

Gosso et al. [16, 67] investigated the association of SNAP-25 with cognitive abilities in a family-based study in two independent Dutch cohorts and found a significant relationship between three SNP's of twelve investigated in the SNAP-25 gene and intelligence measured by the wechsler intelligence scale for children-revised. They discuss a possible role of SNAP-25 in learning and memory imbedded in a superordinated concept of human intelligence. Correspondingly to our study they genotyped the T*ai*I (rs8636) and D*de*I (rs1051312) SNAP-25 polymorphisms, but unfortunately excluded the D*de*I polymorphism due to a missing Hardy–Weinberg equilibrium for further analysis. Comparable to our study, they found no association between the T*ai*I polymorphism and cognitive functioning.

A relation of SNAP-25 to intelligence is also supported by a result in our study, as homozygote T allele carriers of the D*de*I polymorphism had a higher score in the MWT-B test, a measure of "crystallised intelligence", than patients in the combined TC/CC genotype group.

An obvious association of SNAP-25 to human intelligence does not exclude a possible etiological role in schizophrenia. On the contrary, specific cognitive deficits in schizophrenia seem to be associated with intellectual functioning [55] and both concepts were further attributed to partly overlapping neurobiological substrates such as the prefrontal and temporal regions as well as the hippocampal formation [20]. Since an altered glutamatergic or dopaminergic neurotransmission has been implicated as a functional substrate for psychotic and cognitive symptoms in schizophrenia, SNAP-25, as an integral part of synaptic transmission, may contribute to the risk for schizophrenia by affecting cognitive abilities.

A limitation of our study is that it has a retrospective design with an explorative character. Patients were participants of different randomized, double-blind parallel-group designed or open-label studies and were assigned to therapy with different atypical antipsychotics. As it has been reported that atypical antipsychotics with different receptor profiles and effects on psychopathology can also have different effects on cognitive domains [17, 38, 50, 53, 54], the presence of different atypical antipsychotics in genotype groups could have influenced the neuropsychological test results. In our study previously untreated patients had significantly better results than pre-treated patients in working memory at baseline and at week 4 or 6 as well as in executive functions at baseline and performed significantly better in the MWT-B. Even though all patients underwent a wash-out period of 2–14 days before randomization in order to reach baseline dopamine receptor occupancy levels, it has also been described that antipsychotics seem to last longer in human brain tissue, maybe for a number of weeks after withdrawal, and even at higher doses than the circulating ones [32].

As many of these patients received conventional antipsychotics, which are considered, at least at higher dosages, to have an unfavourable effect on neurocognitive functioning [5, 29, 39, 64], this could demonstrate a confounding factor. Another explanation might be that pre-treated patients were significantly older, had a longer duration of illness and a higher number of hospitalizations than untreated patients, which indicates an unfavourable course of the disease often combined with more pronounced cognitive dysfunctions.

Since it cannot be excluded that the above mentioned aspects may demonstrate disturbing factors for comparing neurocognitive test results between genotype groups at baseline and during the treatment phase, the observed differences shall be interpreted with caution and have a preliminary character. However, it has to be stressed that there were neither significant differences in percentage distribution of applied antipsychotics nor in the allocation of previously pre- and untreated patients in genotype groups in our study. Therefore it seems to be very unlikely that these two aspects were responsible for the findings of different neurocognitive test results in genotype groups of the SNAP-25 D*de*I polymorphism. Moreover, both possible confounders were used as

covariates in the variance analyses in order to limit possible disturbing effects on the results.

It has to be emphasized that a strength of our study is the relatively high sample size accompanied by an ethnical homogeneity.

In this study we reported an association between the *Dde*I polymorphism of the SNAP-25 gene and cognitive dysfunctions of schizophrenic patients before and during treatment with atypical antipsychotics. The exact nature of the functional relevance of the SNAP-25 protein in the etiology of schizophrenia, especially whether this polymorphism can possibly alter its quantitative or qualitative nature or alternatively may be in linkage disequilibrium with other unidentified functional polymorphisms, remains to be determined in future studies. But there are hints that SNAP-25 may affect cognitive dysfunctions considered to be a putative endophenotype for schizophrenia.

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