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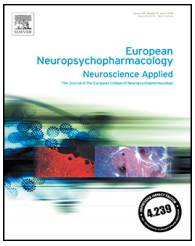

Disparate effects of first and second generation antipsychotics on cognition in schizophrenia – Findings from the randomized NeSSy trial

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Abstract
Cognitive impairment represents a core feature of schizophrenia. Uncertainty about demonstrable benefits of available antipsychotics on cognition remains an important clinical question relevant to patients' quality of life. The aim of our multi-center, randomized, double-blind "Neuroleptic Strategy Study" (NeSSy) was to compare the effectiveness of selected antipsychotics, conventionally classified as second- (SGAs) (haloperidol, flupentixol) and first generation antipsychotics (FGAs) (aripiprazole, olanzapine, quetiapine), on quality of life in schizophrenia. The effects on cognitive deficits represented a secondary outcome. We used an innovative double randomization for assignment of treatment group, and followed the patients with a neurocognitive test-battery upon six and 24 weeks of treatment. Psychopathology and quality of life were assessed using CGI, PANSS and SF-36. Assessment of cognitive performance was conducted in 114 of the 136 randomized patients. The SGA group ($N = 62$) showed beneficial effects of small to moderate effect size on cognition during the initial six weeks of treatment (executive functions, verbal fluency) and at 24 weeks (executive functions, working memory). In contrast, the FGA group ($N = 52$) showed moderately improved executive function, but a decline in verbal fluency at six weeks, with significant declines of moderate to large effect size in executive function, verbal learning and memory, and verbal fluency at 24 weeks. Our study indicates that SGAs present an advantage over FGAs regarding cognitive function during a medium-term treatment for schizophrenia. The results further emphasize a distinction between progression to detrimental effects of FGAs with prolonged treatment in contrast to more persistent cognitive benefits with SGA treatment.

1. Introduction

Development of new strategies for ameliorating cognitive impairments in patients with schizophrenia represents a major clinical challenge. Although not included among the criterion "A" of schizophrenia in DSM-5 (Barch et al., 2013), cognitive deficits are nonetheless a core feature of this most severe of psychiatric illnesses (Keefe et al., 2007a), being detectable in almost all individuals with diagnosis of schizophrenia (Keefe and Harvey, 2012). Cognitive impairments often precede the onset of psychosis (Jones et al., 1994) and can persist during the entire course of the illness (Nuechterlein et al., 1992). Furthermore, cognitive impairments are considered the most predictive factor of functional outcome in terms of social, occupational, and living status (Green et al., 2004; Joseph et al., 2017; Kurtz et al., 2008; McClure et al., 2007; Rajji et al., 2014), medication adherence and ability to self-manage medication (Donohoe et al., 2001; Jeste et al., 2003; Patterson et al., 2002), as well as relapse prevention (Trapp et al., 2013). Nevertheless, cognitive impairments per se seem largely independent of the severity of psychotic symptoms (Keefe et al., 2006; Keefe and Harvey, 2012), which may suggest distinct pathomechanisms underlying positive symptoms and cognitive impairments in schizophrenia.

While directed mainly against the positive symptoms, antipsychotic medication can alleviate or exacerbate cognitive impairments in schizophrenia, although the cognitive profiles of different compounds remain poorly defined (Hori et al., 2006). Up to now, numerous investigations in this field targeted the distinction of different antipsychotics regarding their effectiveness against cognitive symptoms without solving this ambiguity. In the majority of such investigations antipsychotics were classified as first (FGA) and second generation (SGA) antipsychotics, despite the contemporary efforts of the scientific community to optimize the psychopharmacological classification by using the neuroscience based classification (NbN) (Zohar et al., 2014). Results of some treatment studies showed absent or small therapeutic effects of FGA on different cognitive domains (Bowie and Harvey, 2005; Mishara and Goldberg, 2004), whereas some studies indicated some pro-cognitive effects of SGA as compared to FGA treatment (Harvey and Keefe, 2001). Indeed, a certain superiority of some SGA has been reported in two recent meta analyses (Desamericq et al., 2014; Zhang et al., 2013), while a larger most recent meta analysis including 37 studies with 3526 patients (Nielsen et al., 2015) has not shown any drug having a uniform positive cognitive profile but detected trends favoring some SGAs (sertindole, ziprasidone, risperidone, quetiapine) towards FGAs.

On the other hand, two prominent and comprehensive studies – the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) (Keefe et al., 2007b; Lieberman et al., 2005) and the Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia trail (CUtLASS) (Jones et al., 2006) – reported no differences between FGA and SGA treatment regarding cognitive function. Furthermore, an exploratory analysis of cognitive performance after 18 months in the CATIE trial showed greater cognitive improvement with the FGA perphenazine than with the SGAs olanzapine or risperidone (Keefe et al., 2007a). Nonetheless, due *inter alia* to several methodological weaknesses subsequently discerned in those studies (Leucht et al., 2009; Tandon et al., 2007), there has been no consensus regarding the treatment of choice for optimal cognitive outcome.

Given this background, we chose to re-examine in the Neuroleptic Strategy Study (NeSSy) the advantages and disadvantages of SGA versus FGA treatment for cognitive per-

formance in schizophrenia patients. The study was conducted without any sponsorship from industry and employed an entirely novel randomization method, which allowed the therapists to have some influence on the treatment selection for individual patients, despite a strictly double blind design (Schulz et al., 2016). We have recently reported the primary outcome parameters, i.e. the change in total quality-of-life scores from baseline to week 24 after randomization – assessed by using the Short Form 36 Health Survey (SF-36) (Tarlov et al., 1989) and the Clinical Global Impression-Improvement scale (CGI-I) (Guy et al., 1976). In brief, SGAs proved significantly superior to FGAs with respect to patient-reported quality of life (Gründer et al., 2016). We now test our secondary hypothesis that SGAs would likewise prove superior to FGAs in ameliorating the cognitive impairments seen in our patients with schizophrenia.

2. Experimental procedures

After obtaining approval from the responsible human research ethics committees (leading committee: Ethikkommission des Landes Bremen, approval number: EK HB 2009-10-041 FF), this multicenter study was conducted at 14 university and state psychiatric clinics and hospitals in Germany, using a double-blind, double-dummy, randomized design. All directives, guidelines and regulatory requirements, as proposed by the World Medical Association Declaration of Helsinki, the International Conference on Harmonization (ICH), the Good Clinical Practice (GCP), and the ICMJE Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals were fulfilled. The Competence Center for Clinical Trials of the University of Bremen (KKSB) was responsible for project management, monitoring, data management, and statistical data analysis in accordance with the pre-specified study protocol (NeSSy study protocol. Dec 5, 2012).

2.1. Subjects

Patients with a diagnosis of schizophrenia (ICD-10: F20.X) aged between 18 and 65 years, were informed about the possibility of participation if they met clinical need for initiation of a new or modified antipsychotic treatment. We carefully examined all potential participants for exclusion criteria, which included treatment on an involuntary legal basis, acute suicide risk, known hypersensitivity or profound intolerability of any of the study drugs, history of neuroleptic malignant syndrome, severe or chronic somatic diseases, and clinically relevant abnormalities in the standard laboratory tests or electrocardiogram. For female participants of reproductive age, we required a negative pregnancy test and use of reliable contraception. Psychostimulant abuse, but not cannabis abuse was an exclusion criterion. An essential condition for inclusion was provision of written informed consent. All ICMJE Recommendations for the Protection of Research Participants were respected. The recruitment period lasted from April 1, 2010 until May 31, 2013.

2.2. Study design

Patients were randomly allocated to the FGA or SGA treatment strategy using a random number table (block length 30), generated by the KKSB. The enrolment of the participants and their assignment to the interventions were conducted by the study physicians working at each study center. The FGA groups were treated with haloperidol or flupentixol, while the SGA groups received olanzapine, aripiprazole, or quetiapine. The selection of these five specific compounds was based on their widespread use in Europe for treatment of schizophrenia, as well as on their pharmacological disparity, representing five structural classes. The randomization process for each individual patient consisted of two steps, which are described in detail elsewhere (see Schulz et al., 2016).

The study drugs were given twice a day (AM and PM), with one administration consisting of active drug and the second being a placebo. This double-dummy design was necessary to enable the morning application of aripiprazole and the evening application of the other drugs, which have a more sedative profile. Each daily dose consisted of between 2 and 4 capsules, depending on the severity of psychopathology and individual tolerance. The content of a single tablet was either placebo or 5 mg aripiprazole, 3 mg flupentixol, 1.5 mg haloperidol, 5 mg olanzapine or 200 mg quetiapine. Preceding psychopharmacological medication was tapered off during the first two weeks of study-participation, during which time the study-medication was administered at an initial daily dose of one active tablet per day. The only additional psychotropic substances allowed in the study were lorazepam (max. 7.5 mg/day) and biperiden (max. 8 mg/day), as required. Patients had treatment as usual with non-psychotropic drugs for non-psychiatric medical conditions. The whole treatment period was scheduled for 24 weeks. Reasons for premature termination were occurrence of major or intolerable adverse events, failure of therapeutic response (practitioners' decision) or the decision of the patient. The follow-up period after cessation of treatment was scheduled for another 24 weeks.

Therapeutic drug monitoring was conducted at weeks 6 and 24 (visit 4 (V4) and visit 6 (V6)) from the start of randomization (baseline). To ensure adherence to the double-blind design, practitioners were informed only if the measured plasma concentration was below, within or above the therapeutic reference range as defined in the European consensus guideline on therapeutic drug monitoring of psychotropic drugs (Hiemke et al., 2011).

2.3. Assessment of neurocognitive performance

Baseline assessment of neurocognitive performance was made at V0 (prior to the first drug intake), with follow-ups at V4 (scheduled for the sixth treatment week) and V6 (scheduled for the 24th treatment week or, in case of premature termination, on the last treatment day). The neurocognitive test-battery was designed to assess cognitive domains known to be impaired in schizophrenia (Nuechterlein et al., 2008), i.e. the Trail Making Test (TMT), parts A and B to measure performance speed, mental flexibility and executive functions (Reitan, 1958),

Verbaler Lern- und Merkfaehigkeitstest (VLMT) to measure verbal memory (Helmstaedtler et al., 1990), Regensburger Wortfluessigkeitstest (RWT) to measure verbal fluency (Aschenbrenner et al., 2000), and the Letter-Number Span test of working memory performance (Gold et al., 1997). During V0, the patient's premorbid intelligence was estimated using the multiple choice-vocabulary intelligence test (Mehrfachwahl-Wortschatz Intelligenztest, MWT-B) (Lehrl et al., 1977). Psychopathology was assessed using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). Furthermore, for the assessment of clinical functioning and quality of life, we administered the Short Form 36 Health Survey (SF-36) (Tarlov et al., 1989) and the Clinical Global Impression-Severity scale (CGI-S) scale (Guy et al., 1976). For assessment of fitness to enter the study, we obtained baseline measurement of blood chemistry, vital signs and electrocardiograms, and recorded any adverse events.

2.4. Statistical analysis

Statistical analysis was performed on data from the 114 patients who received at least one dose of the study drug and underwent at least one neuropsychological test (intention-to-treat population). Thereby SAS statistical analysis software package, SAS Version 9.4 (SAS Institute, Cary, NC, USA) was used. The demographic characteristics of the included patients, i.e. age, sex, diagnosis, and duration of disease (Table 1), as well as baseline psychopathological and clinical scores (PANSS, CGI-S and SF36) were analyzed for homogeneity of group distributions (alpha = 5%, two-sided, Fisher exact test, Mann-Whitney test). No significant inhomogeneities were found. Further details about the composition of the entire NeSSy collective were reported previously in our main publication (Gründer et al., 2016).

Treatment effects in each neurocognitive test were first evaluated in an exploratory manner using the Wilcoxon signed-rank test, with separate pre-post analyses for the FGA and SGA groups. Short-term treatment effects were evaluated by comparing test performance at V4 (6 weeks after baseline) with baseline scores. For the evaluation of the treatment effects after a medium-term period, performance during V6 (24th treatment week) was compared with the baseline scores. A p-value of <0.05 was considered as statistically significant. All tests were two tailed. Results at V6 were also compared with V4. Missing values were not replaced.

In order to compare the extent of the changes directly between the two strategies, we applied a mixed model (Proc mixed) to minimize the effects of missing data. This model allows the incorporation of all available data into one analysis and is thus suitable to minimize the effects of missing data. P-values of <0.05 were considered statistically significant. All tests were two-tailed. Factors in the mixed model were strategy (group), visit (time), and strategy*visit (group*time) interactions. Furthermore, a random effect for the individual patients was incorporated to account for correlations between measurements in the same individual. Age was included as a covariate in the test performance scores. Graphical representations of the data analysis were created with SAS.

For additional analysis, we calculated the summarized z-scores for all cognitive parameters. Here, all test measures (TMT-A, TMT-B, BZT, subscores of VLMT and RWT) were transformed such that higher values consistently corresponded to better cognitive performance. These transformed measures were then converted to standardized scores by setting the sample mean of each measure at baseline to zero and the standard deviation to 1. A composite z-score was then computed as the mean score of the sum of the several standardized scores.

As a supplemental analysis within each medication group equivalent analyses were conducted for each single substance.

In consideration of the relatively small sample size and the exploratory character of this investigation, we refrained from making any correction for multiple testing.

3. Results

3.1. Patients' characteristics and medication

During the period between April 2010 and May 2013 we screened a total of 2374 patients, of whom 149 met all inclusion criteria. Of these 136 (91%) received at least once the study medication – 63 patients within the FGA-group and 73 within the SGA-group. Statistical analysis for the present manuscript was performed using data from 114 subjects (52 FGA and 62 SGA) among those 136 who had also undergone at least one neuropsychological test battery. The tests were not administered to the remaining 22 participants, either because of a very early dropout or due to their inability or unwillingness to perform the tests. The composition of the final groups showed no statistically significant inhomogeneity regarding sex, age, ethnicity, disease duration, cannabis abuse and baseline symptom severity. Allocation to the treatment with a specific medication within the set of treatment strategies is given in Table 2, which also reports the mean duration of medication intake, dosage and serum concentrations, which were measured in blood samples drawn on V4 and V6. The mean concentrations for all medications were within the therapeutic reference ranges as defined by the AGNP consensus guideline on therapeutic drug monitoring of psychotropic drugs (flupentixol 1–10 ng/mL, haloperidol 1–10 ng/mL, aripiprazole 150–500 ng/mL, olanzapine 20–80 ng/mL, quetiapine 100–500 ng/mL) (Hiemke et al., 2018).

To enable comparability between the groups concerning the extent of the antipsychotic intervention, we calculated the chlorpromazine (CPZ) equivalents and the corresponding defined daily doses (DDD) for each substance. Dose equivalents to 100 mg CPZ were according to a recently published method suggested by Andreasen et al. (2010): aripiprazole: 7.97 mg, haloperidol 1.56 mg, olanzapine 5.33 mg, quetiapine 175.5 mg. Only for flupentixol, which is not represented in this work, the CPZ equivalence dose was taken from the Maudsley Prescribing Guidelines (3 mg) (Taylor et al., 2015). Corresponding DDD were calculated for all drugs according the report of Leucht et al. (2016). Following doses were defined as one DDD: aripiprazole 15 mg, flupentixol 6 mg, haloperidol 8 mg, olanzapine 10 mg, quetiapine 400 mg. The calculated values are summarized in

Table 1 Baseline demographics and clinical characteristics of patients, who underwent cognitive testing at least once.

	FGA $N = 52$	SGA $N = 62$	Total $N = 114$
Age	34.71 (10.42)	34.92 (10.6)	34.82 (10.47)
Mean illness duration[a]	6.13 (6.6)	5.2 (6.15)	5.64 (6.36)
Diagnosis (ICD-10)			
F20	0 (0%)	2 (3.23%)	2 (1.77%)
F20.0	51 (98.08%)	55 (88.72%)	106 (93.8%)
F20.1	0 (0%)	1 (1.61%)	1 (0.88%)
F20.3	0 (0%)	2 (3.22%)	2 (1.76%)
F20.8	1 (1.92%)	1 (1.61%)	2 (1.76%)
Missing	0 (0%)	1 (1.61)	1 (0.88%)
Sex			
Male	40 (76.9%)	38 (61.3%)	78 (68.4%)
Female	12 (23.1%)	24 (38.7%)	36 (31.6%)
Smoker			
Yes	34 (65.4%)	44 (71%)	78 (68.4%)
No	17 (32.7%)	17 (27.4%)	34 (29.8%)
Unknown	1 (1.9%)	1 (1.6%)	2 (1.8%)
Basic assessment scores			
CGI-S baseline	5.06 (0.78)	5.1 (0.84)	5.08 (0.81)
SF-36 baseline[c]	78.23 (16.47)	76.03 (13.91)	77 (10.07)
PANSS-total baseline[d]	82.94 (17.44)	79.25 (21.48)	80.95 (19.72)
MWTB[b]	24.53 (5.11)	25.39 (4.59)	25.01 (4.82)

Data are given as mean (SD), or n/N (%) if data not available for all patients with cognitive assessment.
FGAs= first generation antipsychotics.
SGAs= second-generation antipsychotics.
CGI-S= Clinical Global Impression-Severity.
SF-36= Short Form Health Survey.
PANSS= Positive and Negative Syndrome Scale.
BMI= Body-Mass Index.
MWT-B= Mehrfachwahl-Wortschatztest (version B).
[a] Three missing values from the SGA group.
[b] 23 missing values - 12 FGA and 11 SGA.
[c] 8 missing values - 5 from FGA and 3 from SGA.
[d] One missing value from SGA.

Table 2. Concerning the corresponding DDD, patients in the SGA group have had significantly higher average daily DDD than patients in the FGA group (SGA: 1.1 ± 0.5, FGA: 0.8 ± 0.4; $p < 0.001$). The mean daily CPZ equivalent dose did not differ significantly between the two groups ($p = 0.146$). The mean CPZ equivalence total daily dose was higher in the SGA group (SGA: 233 ± 241; FGA: 156 ± 174), without reaching statistical significance ($p = 0.072$). This trend is most likely related to the longer retention of SGA patients in the study, such that they attained higher cumulative doses. Premature termination of treatment (on any time point) occurred in 81% of the patients treated with an FGA and in 74% of the patients treated with an SGA ($p = 0.503$).

The permissible concomitant medication (lorazepam and biperiden) was used sporadically in a very small proportion of the patients (max. in one or 2 patients per strategy). Thereby, the substances were used as an on-demand medication that was consequently omitted on the day of the neurocognitive examination.

At least one cognitive parameter was assessed during visit 0 in 113 patients (84% of the initial group), of which 52 (81%) in the FGA group and 62 (85%) in the SGA group; during visit 4 in 58 patients (43%) - 21 (33%) in the FGA group and 37 (51%) in the SGA group; during visit 6 in 36 (27%) patients (18 (29%) in the FGA group and 18 (25%) in the SGA group). The incompleteness of the cognitive performance dataset reflects the high dropout rate known in antipsychotic trials, and in several cases excessive fatigue or inattention of the patient.

3.2. Neurocognitive performance

All results of the neurocognitive tests measured during V0, V4, and V6 are given in Table 3.

3.2.1. Performance speed, mental flexibility and executive functions

Table 3 shows performance times for TMT (A) and (B), as well as difference scores (TMT(B)-TMT(A)) and ratio scores (TMT(B)/TMT(A)), which are known to be more indicative for executive control abilities (Giovagnoli et al., 1996; Sanchez-Cubillo et al., 2009) and an index of cognitive flexibility relatively independent of manual dexterity (Corrigan and Hinkeldey, 1987; Vazzana et al., 2010).

Table 2 Group characteristics concerning the medication intake.

	N	Mean duration of medication intake (days)	Mean aver. daily dose (mg/d)	CPZ-average dose	CPZ-total	Corresponding average DDD	Visit 4: Mean serum conc. (ng/ml)	Visit 6: Mean serum conc. (ng/ml)
Aripiprazole	17	79.2 ± 66.7	12.9 ± 5.4	1.6 ± 0.7	131.6 ± 135.5	0.9 ± 0.4	165.1 ± 86.6	240.4 ± 285.9
Flupentixol	30	73.9 ± 62.1	6.3 ± 2.4	2.1 ± 0.8	164.3 ± 153.3	1.1 ± 0.4	5.5 ± 3.5	3.8 ± 3.4
Haloperidol	22	53.6 ± 61.7	3.8 ± 1.3	2.5 ± 0.9	144.3 ± 195.5	0.5 ± 0.2	2.1 ± 1.3	2.2 ± 1.5
Olanzapine	18	96.3 ± 66.3	15.5 ± 4.1	2.9 ± 0.8	298.2 ± 235.2	1.6 ± 0.5	45.1 ± 36.3	39.6 ± 28.4
Quetiapine	27	88.7 ± 102.1	470.3 ± 154.6	2.7 ± 0.9	252.6 ± 280.3	1.1 ± 0.4	320.41±207.2	252.14±151.5
FGA	52	65.3 ± 62.1		2.2 ± 0.8	155.8 ± 173.5	0.8 ± 0.4		
SGA	62	88.4 ± 83		2.5 ± 0.9	232.6 ± 240.9	1.1 ± 0.5		
Total		77.8 ± 74.7		2.4 ± 0.9	197.6 ± 215.4	0.9 ± 0.5		
	114							

Data are given as mean±SD.

FGAs= first generation antipsychotics.

SGAs= second-generation antipsychotics.

For each parameter mean values and standard deviations are given (mean ± SD). Dose equivalents to 100 mg of chlorpromazine (CPZ) and corresponding defined daily dose (DDD) were calculated as stated in the result part of the manuscript on the basis of the main average daily dose for each medication. CPZ-total were derivate from the overall dose during the whole treatment period for each patient.

Table 3 Results measured in cognitive tasks obtained during the three visits (Visit 0 (V0), Visit 4 (V4) and visit 6 (V6)) in the two groups with different treatment strategies (FGA and SGA), represented as mean ± standard deviation.

TMT		**V0**		**V4**		**V6**		**V4-V0**		**V6-V0**	
		N	**MW± SD (s)**	***N***	**MW± SD (s)**	***N***	**MW± SD (s)**	***N***	**MW± SD (s)**	***N***	**MW± SD (s)**
TMT-A	**FGA**	*51*	41.41± 16.47	*21*	32.9 ± 11.74	17	31.35±9.71	20	−7.4 ± 13.24	17	−1.41±6.81
	SGA	*59*	40.81± 18.23	*36*	33.83± 13.23	17	36.53± 13.96	35	−4.97±12.15	17	−5.82±11.8
TMT-B	**FGA**	*49*	102.89± 53.25	*20*	79.9 ± 35.71	18	97.33±60.52	19	−23.79±33.04	17	−1 ± 34.4
	SGA	*59*	102.27±55.9	*36*	88.17±33.72	18	79.61±35.89	35	−14.43±41.06	18	−6.61 ± 37.03
TMTB-TMTA	**FGA**	*49*	61.51± 45.86	*20*	47.4 ± 26.37	17	60.65± 54.81	19	−15.58± 26.23	16	−0.31±34.2
	SGA	*59*	61.46± 45.65	*36*	54.33± 28.33	17	45.23±31.1	35	−9.45 ±43.11	17	−1.47±35
TMTB/TMTA Ratio	**FGA**	*49*	2.55±1.02	*20*	2.46±0.59	17	2.96±1.66	19	−0.05±0.68	16	0.15±1
	SGA	*59*	2.56±0.94	*36*	2.74±0.94	17	2.35±0.9	35	0.04±1.26	17	0.08±0.91
VLMT		V0		V4		V6		V4-V0		V6-V0	
		N	MW±SD	*N*	MW±SD	*N*	MW±SD	*N*	MW±SD	*N*	MW±SD
Free recall (round 1)	**FGA**	*41*	5.46±1.89	*17*	5.76±1.43	14	6.0 ± 1.3	16	0.06±0.85	14	−0.07± 1.2
	SGA	*50*	5.74±2.54	*31*	6.64±2.68	11	5.63±3.04	28	0.89±2.88	11	0.55±3.01
Free recall (round 1-5)	**FGA**	*41*	40.34± 11.98	*17*	42.06± 10.07	14	46.07±9.52	16	2.69±7.68	14	1.5 ± 7.73
	SGA	*50*	43.42± 12.78	*31*	46.94± 13.18	11	46.09± 13.47	28	1.86±12.38	11	4.45± 8.91
Loss by interference	**FGA**	*40*	2.12±1.57	*16*	1.94±2.17	13	3.54±2.1	15	−0.27±2.12	13	1.62±2.81
	SGA	*50*	2.84±4.76	*31*	2.61±3.78	11	2.91±2.02	28	−0.75±5.05	11	1 ± 1.73
Loss by delay	**FGA**	*41*	1.83±1.84	*17*	2.65±1.8	14	4.21±3.46	16	0.69±1.89	14	2.21±3.92
	SGA	*49*	2.33±2.15	*31*	2.87±4.82	11	3.09±3.02	28	−0.25±3.09	11	0 ± 3.1
Recognition	**FGA**	*39*	10.33±5.25	*17*	10.53±3.37	13	10.08±4.85	16	0.38±4.45	13	−0.85±3.48
	SGA	*44*	9.68±4.81	*29*	11.38±3.76	11	10.81±3.57	28	0.65±4.54	11	0.27±4.07
LNS		V0		V4		V6		V4-V0		V6-V0	
		N	MW±SD	*N*	MW±SD	*N*	MW±SD	*N*	MW±SD	*N*	MW±SD
	FGA	*41*	13.1 ± 3.6	*17*	13.53±3.26	16	13.0 ± 4.76	15	1.13±2.58	13	0.38±2.72
	SGA	*51*	12.1 ± 3.9	*32*	13.65±3.65	15	14.33±3.66	29	0.68±3.89	13	2.31±4.23

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Table 3 (*continued*)

RWT		V0		V4		V6		V4-V0		V6-V0	
		N	MW±SD	*N*	MW±SD	*N*	MW±SD	*N*	MW±SD	*N*	MW±SD
vf/p (1 min)	**FGA**	*44*	9.14±4.4	*17*	9.53±4.7	14	9.64±6.3	16	0.63±3.77	14	−0.43±4.3
	SGA	*46*	9.17±4.36	*29*	11.13±5	13	11.2 ± 2.74	24	0.75±3.8	12	1.42±3.3
vf/p (2 min)	**FGA**	*43*	14.33±7.4	*15*	14.6 ± 7.21	14	14.78±9.9	15	−0.2 ± 5.77	14	−0.79±5.9
	SGA	*42*	14.6 ± 9.13	*25*	16.4 ± 8.16	12	16.75±6.4	21	−0.33±6.6	11	−0.9 ± 8.6
vf/s (1 min)	**FGA**	*43*	15.9 ± 4.91	*17*	13.1 ± 5.84	14	14.21±4.6	14	−4.1 ± 4.3	14	−3.43±5.4
	SGA	*45*	16.4 ± 4.72	*29*	17.28±5.9	13	17.62±7.9	24	0.04±6.9	12	1.83±6.9
vf/s (2 min)	**FGA**	*42*	24.17±7.6	*16*	20.9 ± 11.1	14	21.5 ± 8.78	14	−5.21±8.13	14	−4.43±6.9
	SGA	*42*	25.2 ± 8.55	*25*	25.24±9.3	12	28.3 ± 14.5	21	−0.95±11.3	11	6 ± 13
cc/p (1 min)	**FGA**	*39*	10.1 ± 4.56	*15*	10.73±3.9	14	11.36±5.2	12	1.17±2.82	14	0.14±2.44
	SGA	*44*	10.14±3.8	*27*	12.26±4.3	12	11.25±3.4	23	2.34±3.9	11	0.2 ± 4.5
cc/p (2 min)	**FGA**	*39*	15.82±7.4	*14*	16.29±6.4	14	17.28±9.1	12	0.00±3.4	14	1 ± 4.2
	SGA	*41*	16.15±6.2	*25*	18.96±7.1	12	17.75±5.1	21	3.47±4.8	11	0.6 ± 4.6
cc/s (1 min)	**FGA**	*39*	10.67±3.1	*15*	9.53±3.5	14	10.14±3.7	12	−1.1 ± 3.9	14	−1.5 ± 3.7
	SGA	*44*	11.23±3.6	*28*	11.89±4.5	12	10.75±4.1	23	0.04±4.2	11	0.4 ± 4.8
cc/s (2 min)	**FGA**	*39*	16.05±5.2	*14*	14.0 ± 5.1	14	13.93±4.6	12	−3.2 ± 4.7	14	−4.78±6.1
	SGA	*42*	17.21±6.1	*25*	16.68±6.3	11	16.81±5.7	21	−0.86±5.84	10	1.2 ± 5.5
Composite *z*-score		V0		V4		V6		V4-V0		V6-V0	
		N	MW±SD (s)	*N*	MW±SD (s)	*N*	MW±SD (s)	*N*	MW±SD (s)	*N*	MW±SD (s)
	FGA	*45*	0.07±0.64	*26*	0.29±0.59	16	0.05±0.47	26	0.13±0.56	16	−0.03±0.6
	SGA	*50*	−0.03±0.1	*25*	0.1 ± 0.76	13	0.31±0.85	24	0.16±0.56	13	0.03±0.48

Abbreviations.
FGA= first generation antipsychotics.
SGA= second-generation antipsychotics.
TMT-A – Trail Making Test, part A.
TMT-B – Trail Making Test, part B.
VLMT – verbal learning and memory test.
LNS – Letter Number Span.
RWT – verbal fluency task (Regensburger Wortfluessigkeitstest).
vf /p – verbal fluency-phonemic.
vf/s – verbal fluency semantic.
cc/p – category change-phonemic.
cc/s – category change semantic.

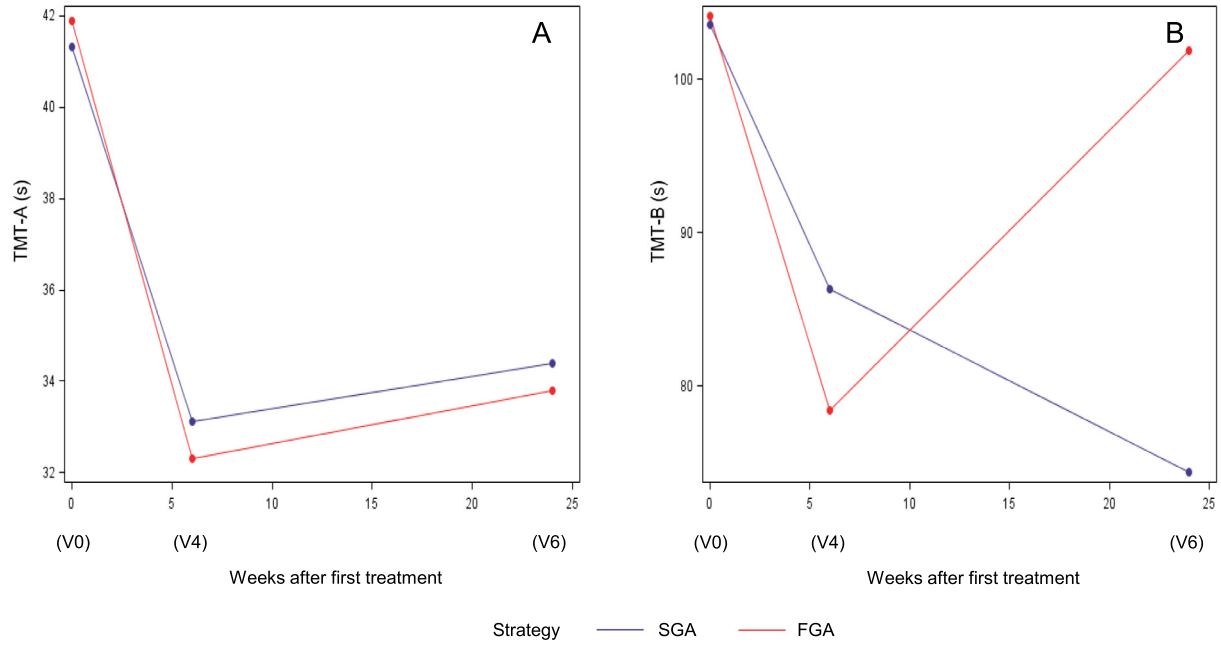

Fig. 1 Results of the Trail Making Test (TMT (A) and TMT (B)) measured on baseline (V0), after 6 weeks (V4) and after 24 weeks (V6) in the two treatment strategies (first-generation (FGA) and second generation (SGA) antipsychotics).

In the exploratory analysis after the initial six weeks treatment period between V0 and V4, we saw a significant improvement in the time to complete both parts of the TMT test (A and B) for both treatment groups (TMT(A): FGA: V0: 41.4 ± 16.5 s, V4: 32.9 ± 11.7 s; $p = 0.009$, ES 0.4; SGA: V0: 40.8 ± 18.2 s, V4: 33.8 ± 13.2 s; $p = 0.022$, ES 0.26; TMT(B): FGA: V0: 102.9 ± 53.4 s; V4: 79.9 ± 35.7 s, $p = 0.004$, ES 0.44; SGA: V0: 102.3 ± 55.9 s, V4: 88.2 ± 33.7 s, $p = 0.03$, ES 0.26) (Fig. 1). The difference score (TMT(B)-TMT(A)) also significantly declined in the FGA group (V0: 61.5 ± 45.9 s, V4: 47.4 ± 26.4 s; $p = 0.028$, ES 0.35), indicating an improvement of executive functions (Table 4).

During the further treatment period, the performance in TMT worsened in both groups, approaching statistical significance only in the FGA group for TMT-B: V4: 79.9 ± 35.7 s, V6: 97.3 ± 60.5 s, p = 0.064, ES 0.42. At the final examination (V6), only the performance of the SGA group in the TMT(A) part was improved in comparison to baseline in an almost statistically significant extent (V6: 36.5 ± 14.0 s, V0: 40.8 ± 18.2 s; $p = 0.081$, ES 0.3). The results of the exploratory analysis were confirmed by a mixed model analysis of variance with age as a covariate, which showed a statistically significant interaction between group and time for the variables TMT(A) ($p = 0.0012$) and TMT(B) ($p = 0.0098$) (Table 5).

3.2.2. Verbal memory

VLMT (Verbaler Lern- und Merkfaehigkeitstest) test results are also given in Table 3. There were no significant changes during the short-time treatment period (V4-V0) in the FGA and SGA groups. There was a trend towards improvement of the free recall for the SGA group in the first query session (V0: 5.74 ± 2.54, V4: 6.64 ± 2.68, $p = 0.072$, ES 0.24) and recognition (V0: 9.68 ± 4.81, V4: 11.38 ± 3.76, $p = 0.088$, ES 0.24) (Table 4).

After the longer treatment period, in the V6 we saw a significant deterioration in the FGA group for the parameters memory loss through interference (V0: 2.12 ± 1.57, V6: 3.54 ± 2.1, $p = 0.035$, ES 0.4) and memory loss by delay (V0: 1.83 ± 1.84, V6: 4.21 ± 3.46, $p = 0.01$, ES 0.47) (Fig. 2). In the SGA group, all test parameters did not change significantly in comparison with the baseline scores. In the mixed model analysis of variance, with age as covariate, only the strategy*visit interaction for the parameter loss by delay showed a trend, although without reaching statistical significance ($p = 0.09$) (Table 5).

3.2.3. Working memory performance

In the letter-number span there was a trend towards improvement at V6 in the SGA group (V0: 12.1 ± 3.9; V6: 14.3 ± 3.7, $p = 0.078$, ES 0.35).

3.2.4. Verbal fluency

Exploratory analysis of the verbal fluency task (Regensburger Wortfluessigkeitstest (RWT)) revealed a performance deterioration to V4 in the FGA group in the categories of semantic fluency after one minute (V0: 15.9 ± 4.91, V4: 13.1 ± 5.84, $p = 0.003$, ES 0.53) and two minutes (V0: 24.17 ± 7.6, V4: 20.9 ± 11.1, $p = 0.038$; ES 0.39), as well as in the semantic category change after two minutes (V0: 16.05 ± 5.2, V4: 14.0 ± 5.1, $p = 0.035$; ES 0.43). In contrast, the SGA group showed significant improvement in their performance of *phonemic category change* after one minute (V0: 10.14 ± 3.8, V4: 12.26 ± 4.3, $p = 0.01$; ES 0.37) and after two minutes (V0: 16.15 ± 6.2, V4: 18.96 ± 7.1, $p = 0.006$; ES 0.41). The comparison between the score differences (V4-V0) of the two strategies was statistically significant for the category *semantic fluency* after one minute ($p = 0.021$, ES 0.37).

Table 4 Results of an explorative analysis of the cognitive performance in patients treated with the different antipsychotic strategies.

TMT		**V4 vs. V0**		**V6 vs. V0**		**V6 vs. V4**	
		p	*r*	*p*	*r*	*p*	*r*
TMT-A	**FGA**	**0.009***	0.40	0.503	0.12	0.915	0.03
	SGA	**0.022***	0.27	**0.081**	0.3	0.130	0.28
	FGA vs. SGA	0.575	0.08	0.227	0.21	0.466	0.14
TMT-B	**FGA**	**0.004***	0.44	0.738	0.06	**0.064**	0.42
	SGA	**0.030***	0.26	0.436	0.13	0.480	0.13
	FGA vs. SGA	0.355	0.13	0.680	0.07	0.384	0.17
TMTB-TMTA	**FGA**	**0.028***	0.35	0.945	0.02	0.105	0.38
	SGA	0.340	0.12	0.990	0.01	0.680	0.08
	FGA vs. SGA	0.323	0.13	1	0.01	0.318	0.2
TMTB/TMTA Ratio	**FGA**	0.984	0.01	0.669	0.08	0.322	0.24
	SGA	0.824	0.03	0.644	0.09	0.934	0.02
	FGA vs. SGA	0.765	0.04	0.914	0.02	0.292	0.21
VLMT		V4 vs. V0		V6 vs. V0		V6 vs. V4	
		p	*r*	*p*	*r*	*p*	*r*
Free recall- first session	**FGA**	0.763	0.05	0.875	0.05	0.750	0.18
	SGA	**0.072**	0.24	0.641	0.12	0.055	0.44
	FGA vs. SGA	**0.097**	0.25	0.510	0.13	**0.076**	0.42
Free recall total	**FGA**	0.470	0.13	0.626	0.1	0.578	0.17
	SGA	0.302	0.14	0.141	0.32	0.111	0.37
	FGA vs. SGA	0.966	0.01	0.310	0.21	0.528	0.16
Loss due to interference	**FGA**	0.670	0.08	**0.035***	0.4	0.375	0.29
	SGA	0.854	0.03	0.102	0.38	0.594	0.17
	FGA vs. SGA	0.823	0.04	0.718	0.08	0.648	0.12
Loss due to delay	**FGA**	0.156	0.25	**0.010***	0.47	0.906	0.05
	SGA	0.426	0.11	0.943	0.15	0.391	0.2
	FGA vs. SGA	0.227	0.18	0.101	0.33	0.986	0.01
Recognition	**FGA**	0.750	0.06	0.422	0.18	0.219	0.34
	SGA	**0.088**	0.23	0.84	0.05	0.313	0.25
	FGA vs. SGA	0.372	0.14	0.921	0.02	0.417	0.2
LNS		V4 vs. V0		V6 vs. V0		V6 vs. V4	
		p	*r*	*p*	*r*	*p*	*r*
	FGA	**0.057**	**0.25**	0.328	0.21	0.281	0.28
	SGA	0.477	0.09	**0.078**	0.35	0.884	0.05
	FGA vs. SGA	0.375	0.14	0.563	0.12	0.543	0.13
RWT		V4 vs. V0		V6 vs. V0		V6 vs. V4	
		p	*r*	*p*	*r*	*p*	*r*
vf/p (1 min)	**FGA**	0.833	0.04	0.648	0.09	0.766	0.11
	SGA	0.389	0.13	0.215	0.27	0.934	0.03
	FGA vs. SGA	0.795	0.04	0.212	0.25	0.659	0.11
vf/p (2 min)	**FGA**	0.766	0.06	0.897	0.03	0.906	0.06
	SGA	0.790	0.04	0.904	0.03	0.854	0.08
	FGA vs. SGA	0.8	0.05	0.809	0.05	0.962	0.01
vf/s (1 min)	**FGA**	**0.003***	0.53	**0.031**	**0.4**	0.375	0.29
	SGA	0.816	0.04	0.402	0.18	0.536	0.14
	FGA vs. SGA	**0.021***	0.37	**0.076**	0.36	0.86	0.04
vf/s (2 min)	**FGA**	**0.038***	0.39	**0.020**	0.43	**0.063**	0.54
	SGA	0.629	0.08	0.269	0.25	0.910	0.04
	FGA vs. SGA (p/r)	0.293	0,18	**0.029***	0.43	0.315	0.25
cc/p (1 min)	**FGA**	0.109	0.34	0.736	0.08	0.75	0.11
	SGA	**0.010**	0.37	1	0.01	**0.047***	0.45
	FGA vs. SGA	0.644	0.08	0.893	0.03	0.193	0.33

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Table 4 (*continued*)

cc/p (2 min)	**FGA**	0.815	0.05	0.20	0.25	0.813	0.12
	SGA	**0.006***	**0.41**	0.938	0.01	0.262	0.27
	FGA vs. SGA	0.113	0.28	0.344	0.19	0.601	0.13
cc/s (1 min)	**FGA**	0.369	0.2	0.193	0.26	0.813	0.11
	SGA	0.997	0.01	0.722	0.01	0.848	0.05
	FGA vs. SGA	0.668	0.08	0.467	0.16	0.813	0.07
cc/s (2 min)	**FGA**	**0.035***	**0.43**	**0.027***	0.42	0.625	0.18
	SGA	0.377	0.14	0.629	0.12	0.688	0.11
	FGA vs. SGA	0.518	0.12	**0.026***	0.46	0.813	0.07

Composite z-score		V4 vs. V0		V6 vs. V0		V6 vs. V4	
		p	*r*	*p*	*r*	*p*	*r*
	FGA	0.367	0.11	0.918	0.01	**0.088**	0.26
	SGA	**0.037***	0.24	0.972	0.01	**0.05***	0.32
	FGA vs. SGA	0.437	0.11	0.792	0.01	0.875	0,04

Abbreviations:
FGA= first generation antipsychotics.
SGA= second-generation antipsychotics.
TMT-A - Trail Making Test, part A.
TMT-B - Trail Making Test, part B.
VLMT - verbal learning and memory test.
LNS - Letter Number Span.
RWT - verbal fluency task (Regensburger Wortfluessigkeitstest).
vf /p - verbal fluency-phonemic.
vf/s - verbal fluency semantic.
cc/p - category change-phonemic.
cc/s - category change semantic.
Comparison between the scores in visit 4 respective visit 6 and scores achieved at baseline in each group were performed using the Wilcoxon signed-rank test. Statistically significant results ($p \leq 0.05$) are marked with asterisks. They are given in bold print, as well as values approaching significance ($p < 0.1$). Wilcoxon test was also used to compare the two groups concerning the performance difference calculated between visit 4 and visit 0, visit 6 and visit 0 respective visit 6 and visit 4. Effect sizes (ES) were calculated using the formula: $r = Z/\sqrt{N}$. as proposed by Rosenthal, 1994.

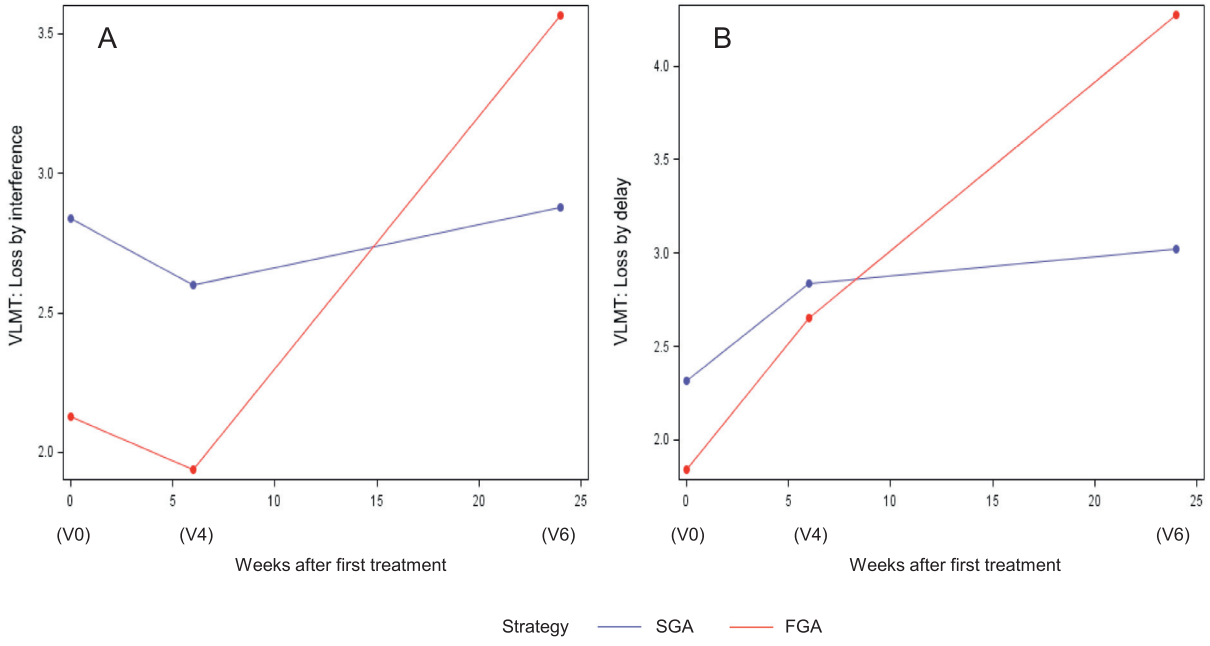

Fig. 2 Results of the verbal memory (verbal learning and memory test, VLMT) measured on baseline (V0), after 6 weeks (V4) and after 24 weeks (V6) in the two treatment groups (first-generation (FGA) and second generation (SGA) antipsychotics). Depicted are the results for the parameters loss by interference (A) and loss by delay (B).

Table 5 Strategy*visit interaction for assessed cognitive parameters as a results of mixed-model ANOVA. For each Variable effects of age were considerate as a covarite.

		Num DF	Den DF	*F*	*p*
TMT-A/ TMT-B	**TMT-A**	4	194	4.69	**0.0012****
	TMT-B	4	193	3.43	**0.0098****
	TMTB-TMTA	4	191	1.80	0.13
	TMTB/TMTA	4	191	0.88	0.48
VLMT	**Free recal**	4	157	1.07	0.37
	Loss by interference	4	154	1.02	0.39
	Loss by delay	4	156	1.99	0.09
	Recognition	4	146	0.91	0.46
BZT		4	165	1.79	0.13
RWT	**vf/p (1 min)**	4	156	1.46	0.217
	vf/p (2 min)	4	144	0.51	0.728
	vf/s (1 min)	4	154	1.14	0.342
	vf/s (2 min)	4	144	0.66	0.624
	cc/p (1 min)	4	144	1.84	0.125
	cc/p (2 min)	4	138	1.12	0.349
	cc/s (1 min)	4	145	0.49	0.743
	cc/s (2 min)	4	138	0.65	0.627
Composite z-score		4	200	1.79	0.132

Abbreviations:
TMT-A - Trail Making Test, part A.
TMT-B - Trail Making Test, part B.
VLMT - verbal learning and memory test.
LNS - Letter Number Span.
RWT - verbal fluency task (Regensburger Wortfluessigkeitstest).
vf /p - verbal fluency-phonemic.
vf/s - verbal fluency semantic.
cc/p - category change-phonemic.
cc/s - category change semantic.

At V6, the FGA group demonstrated statistically significant performance decline for the categories of *semantic fluency after one* ($p = 0.031$; ES 0.4) and *two minutes* ($p = 0.02$; ES 0.43) as well as for semantic category *change* after two minutes ($p = 0.027$; ES 0.42). The score changes to V6 within the SGA group failed to reach statistical significance in any category, but score changes to V6 differed between the treatment groups for the categories *semantic fluency after two minutes* ($p = 0.029$; ES 0.43) and *semantic category change after two minutes* ($p = 0.026$; ES 0.46) (Fig. 3).

3.2.5. Composite z-score

Using the procedure described at the end of the methods section we calculated composite z-scores for all evaluated participants as follows: during V0 ($N = 95$): 0.02 $\pm$ 0.62, during V4 ($N = 51$): 0.2 $\pm$ 0.68, and during V6 ($N = 29$): 0.17 $\pm$ 0.67. Values for FGAs and SGAs are shown in Table 3, and values for each single substance are presented as supplemental material (Supplement, Table 2s). In the FGA treated patients a trend like deterioration in global cognition ($p = 0.088$) between V4 (0.29 $\pm$ 0.59) and V6 (0.05 $\pm$ 0.47) was observable, while in SGA treated patients scores on global cognition improved significantly ($p = 0.037$) between V0 (-0.03 ± 0.1) and V4 (0.1 $\pm$ 0.76) and also between V4 and V6 (0.31 $\pm$ 0.85; $p = 0.05$).

The z-score differences between V4 and V0 (0.14 $\pm$ 0.56, $N = 50$) in the whole sample slightly missed to reach a statistically significant correlation with the change of the self-rated subjective condition grasped with the SF36 scale ($r = 0.397$, $p = 0.074$). Here again, the correlation with changes in the subscale for mental well-being (SF 36-mental) was statistically significant ($r = 0.453$; $p = 0.039$). The z-score differences did not correlate with changes in the PANSS total or any PANSS subscore,

3.2.6. Cognitive performance within the single medication groups

In order to acknowledge the different modes of action of the single drugs within the FGA and SGA strategy and considering the suggested neuroscience based nomenclature (NbN), we analyzed the cognitive outcome in each single medication group separately (Zohar et al., 2014; Zohar and Kasper, 2016). The test results and results of the corresponding statistical analysis are shown in the supplementary material as Tables 1s and 2s.

Patients treated with aripiprazole (NbN: pharmacological domain: dopamine, serotonin; mode of action: D_2 and 5-HT_{1A} receptor partial agonist, 5-HT_{2A} receptor antagonist) showed a significant improvement in VLMT during the first 6 weeks of treatment (Free recall- first session V0: 4.85 $\pm$ 2.54, V4: 7.43 $\pm$ 2.7 ($p = 0.027$, ES 0.49); free recall total

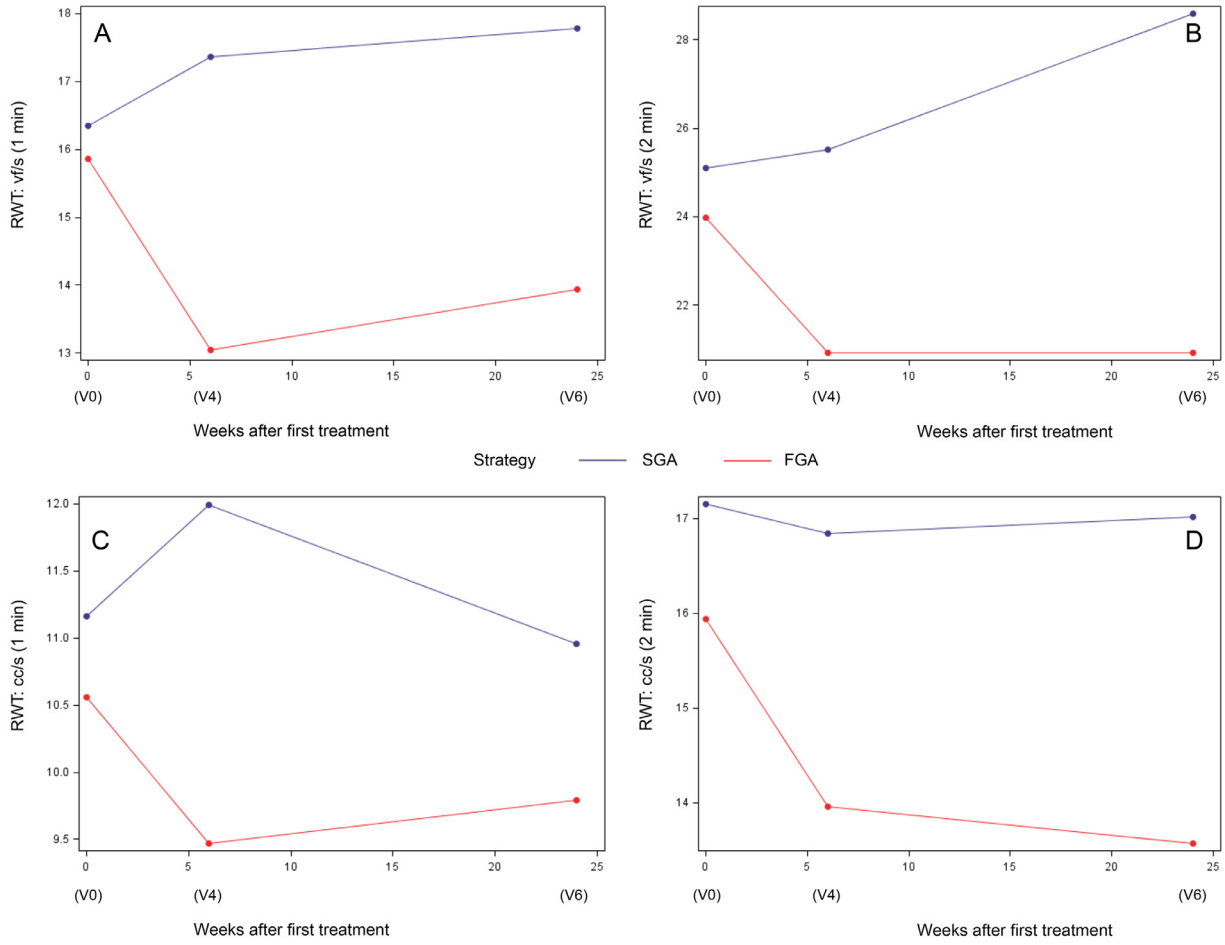

Fig. 3 Results of the verbal fluency (Regensburg Test for Verbal Fluency) measured on baseline (V0), after 6 weeks (V4) and after 24 weeks (V6) in the two treatment groups (first-generation (FGA) and second generation (SGA) antipsychotics). Results are depicted for the parameters *semantic verbal fluency during one minute* (vf/s (1 min)) (A) and *during two minutes* (vf/s (2 min)) (B) as well as *semantic category change during one minute* (cc/s (1 min) (C) and *during two minute*s (cc/s (2 min) (D).

(V0: 41.3 ± 11.88, V4: 49.14 ± 12.29, $p = 0.028$, ES 0.49). For both variables the performance after 24 weeks further improved (Free recall- first session V6: 8 ± 4.36; free recall total: V6: 54 ± 14.8), although the small sample size in the last session hampered the statistical validation of this improvement. Further, a trend like statistical improvement could be shown for the semantic verbal fluency (V0: 22 ± 9.9; V4: 26.6 ± 10.15; $p = 0.068$, ES 0.43).

Patients treated with flupentixol (NbN: pharmacological domaine: dopamine, serotonin; mode of action: D_2 and 5-HT_2 receptor antagonist) showed a significant improvement in executive functioning within the first 6 treatment weeks (TMT-A: V0: 38.73 ± 14.68, V4: 32.07 ± 2.91, $p = 0.005$ (ES 0.43); TMT-B: V0: 100.14 ± 54.09, V4: 80.77 ± 39.97, $p = 0.03$ (ES 0.3)). The TMT-B performance decreased after 24 treatment weeks (V6: 103.3 ± 67.63), though without reaching statistical significance. The semantic verbal fluency (RWT) decreased in the short time observation period (V0: 16.79 ± 5.6; V4: 13 ± 6.37; $p = 0.0015$ (ES 0.4)). In contrast, the working memory performance improved significantly in both observation periods: (V0: 13.48 ± 3.78; V4: 14.08 ± 3.12; $p = 0.021$ (ES 0.38); V6: 14.3 ± 5; $p = 0.042$ (ES 0.34)).

In the group treated with haloperidol (NbN: pharmacological domain: dopamine; mode of action: D_2 receptor antagonist) a performance decrease on trend level was observed in the semantic category change after longer term treatment (V: 10.24 ± 3.38; V6: 8 ± 3.54; $p = 0.068$ (ES 0.39).

Patients treated with olanzapine (NbN: pharmacological domain: dopamine, serotonin; mode of action: D_2 and 5HT2 receptor antagonist) showed a significant improvement in executive functioning within the first 6 treatment weeks (TMT-B: V0: 111.81 ± 39.08, V4: 83.81 ± 24.3, $p = 0.022$ (ES 0.44)), as well as an improvement on trend level in the VLMT (recognition improved V0: 9.08 ± 5.2, V4: 11.75 ± 2.05; $p = 0.084$; ES 0.35). Further, they showed an improvement in phonemic category change after 6 treatment weeks (after 1 min: V0: 8.85 ± 2.96; V4: 12.13 ± 3.31; $p = 0.028$, ES 0.48; after 2 min: V0: 14.54 ± 5.06; V4: 17.38 ± 5.8; $p = 0.028$, ES 0.48) and in semantic verbal fluency after 24 weeks (after 1 min: V0: 15.38 ± 5.32; V6: 18.67 ± 6.15; $p = 0.043$, ES 0.46; after 2 minute: V0: 22.54 ± 9.04; V6: 31.5 ± 14.65; $p = 0.027$; ES 0.051).

In patients treated with quetiapine (NbN: pharmacological domain: dopamine, serotonin, noradrenaline; mode of action: D_2 and 5HT_2 receptor antagonist and NET reuptake

inhibitor) significant improvement was apparent in phonemic category change after 6 treatment weeks (after 2 min: V0: 17.22 ± 7.28; V4: 22.08 ± 6.68; $p = 0.05$, ES 0.33) as well as a trend towards TMT-A improvement after 24 weeks (V0: 43.48 ± 21.74, V4: 28.25 ± 10.62, $p = 0.068$, ES 0.33).

3.3. Changes of general psychopathology and well-being

The changes of general psychopathology and PANSS scores in the whole sample were reported in the main publication (Gründer et al., 2016). To emphasize the relationship between cognitive performance and psychopathology we herein report the PANSS scores only in those participants who also underwent neuropsychological testing (Supplement, Table 3s) during V0 ($N = 113$), V4 ($N = 58$) and V6 ($N = 36$). In addition to the three classically used factors (positive syndrome, negative syndrome and general psychopathology) of Kay et al. (1987), we also calculated scores for the component disorganization symptoms of van der Gaag et al. (2006). This score is thought to be inversely correlated with cognitive function (Minor and Lysaker, 2014); it includes the items stereotyped thinking (N7), poor attention (G11), disorientation (G10), conceptual disorganization (P2), difficulty in abstraction (N5), mannerism (G5), lack of judgment and insight (G12), disturbance of volition (G13), preoccupation (G15) and unusual thought content (G9).

At baseline, none of the psychopathology scores differed significantly between the FGA and the SGA group. At the end of the treatment (V6), we found statistically significant differences between the two treatment strategies for PANSS total score (FGA: 57.5 ± 16.9, SGA: 46.3 ± 14.1; $p = 0.039$, ES 0.35), PANSS positive (FGA: 12.9 ± 5.7; SGA: 9.9 ± 4.6; $p = 0.043$, ES 0.34), PANSS negative (FGA: 17.7 ± 6.5, SGA: 13.1 ± 4.9; $p = 0.03$, ES 0.36), PANSS disorganization symptoms (FGA: 18.4 ± 5.7, SGA: 14.4 ± 5.3; $p = 0.025$, ES 0.38) and CGI-S (FGA: 3.8 ± 0.9, SGA: 3.0 ± 1.2; $p = 0.033$, ES 0.36).

Subjective well-being scores in the SF36 did not differ significantly between the FGA and SGA group at baseline. At V6, the SGA group expressed a better general subjective condition to the SF36 self-assessment (FGA: 83.8 ± 17.6; SGA: 97.9 ± 11.0; $p = 0.04$, ES 0.42).

Relevant tardive dyskinesia (according to the Schooler-Kane criteria (Schooler and Kane, 1982)), which could be predictive for lack of neurocognitive response to antipsychotic treatment (Caroff et al., 2011), was detected only in four patients at baseline (two in the haloperidol group, one in the flupentixol group and one in the olanzapine group).

Detailed information about adverse events and side effects, which did not differ statistically significantly between the FGA and SGA groups, is provided in our main publication of the NeSSy study (Gründer et al., 2016)

4. Discussion

In this multicenter study employing a novel double blind, double dummy design, with double randomization, we aimed to compare the effects of typical (FGA) and atypical (SGA) antipsychotics on cognitive functions in schizophrenia. We found beneficial effects on cognition with a small to moderate effect size in the SGA group during the six weeks' short-term treatment period and at 24 weeks. While FGA treatment initially improved certain executive functions, there was a decline relative to baseline of moderate to large effect size at 24 weeks.

Our findings of cognitive improvement with SGA are in accordance with previous reports showing small beneficial effects for olanzapine (Keefe et al., 2004), quetiapine (Hashimoto et al., 2015; Johnsen et al., 2013), risperidone (Keefe et al., 2007b) and aripiprazole (Schlagenhauf et al., 2010). In particular, improvement in cognitive function during clozapine treatment was replicated several times (Galletly et al., 2000; Hagger et al., 1993; Molina et al., 2014). Furthermore, a meta-analysis indicated that SGAs were superior with respect to overall cognitive function (ES 0.24), particularly for the domains *learning and processing speed* (Woodward et al., 2005), as recapitulated for general cognition in more recent meta-analyses (Desamericq et al., 2014; Zhang et al., 2013). Another larger meta-analysis did not reveal any general differences between FGAs and SGAs on the composite cognitive score and also did not show a uniform positive cognitive profile for any of the observed antipsychotics. However, certain trends in favor of some SGAs were detected as well as superior effects of sertindole compared to clozapine, quetiapine, and FGAs; yet these results were primarily driven by one single small study (Nielsen et al., 2015). Regarding the mechanisms underlying the beneficial effects of SGAs on cognition, several pathways beyond the dopaminergic were proposed (Meltzer, 2015), but this will not be further discussed in this work.

Practice effect can improve performance of conventional neuropsychological tests administered with test-retest intervals of weeks, or years (Collie et al., 2003), notably between the first and second administrations of the test battery. Several authors reported a significant improvement in executive functions by practice effects (Bird et al., 2004; Bartels et al., 2010; Beglinger et al., 2005) in healthy, well-performing subjects. A lack of a placebo group in our study makes it impossible to measure the effects of practice in our schizophrenia patients. However, the performance changes from V0 to V4 in the FGA group and to V6 in the SGA group seem unlikely to reflect solely practice effects. There were parallel improvements only in the TMT during the short observation period, whilst the two treatment groups revealed opposite changes for verbal fluency to V4 and in executive functions, verbal fluency and verbal memory to V6. Thus, even if the improvement in the SGA group were due to practice effects, the FGA group showed no such improvement, or indeed blockade of a practice effect. Furthermore, the illness duration, as a potential indicator of previously performed cognitive examinations during the course of illness (for diagnostic purposes) and additional practice effects had no influence on test results or on result changes.

We discern a relevant association between impaired cognitive performance and general well-being arising from adverse medication effects. Thus, small cognitive benefits seen for our SGA group may indicate attenuated adverse effects rather than actual pro-cognitive benefits. Subjective state of health and performance ability ratings showed

significantly higher scores in the SGA group for SF36 at V6. Thus, better cognitive performance in the SGA group was paralleled by higher self-ratings of health and performance ability. We searched for correlations between the change of the total cognitive z-score (at V4 and V6 relative to V0) and changes in the subjective rating scales. This exploratory analysis showed a trend towards significant correlation for the SF 36 total score; while the correlation with changes in the subscale for mental well-being was statistically significant, the subscore for physical well-being was not. This is consistent with earlier findings in a considerably larger sample (Keefe et al., 2007b).

While PANSS is normally evaluated as positive, negative and total scores, the disorganization component score, is thought to represent a clinical manifestation of cognitive deficits (Minor and Lysaker, 2014). This subscore was significantly lower in the SGA group than in the FGA group at V6, indicating better cognitive status; this difference was absent at V0, implying that overall cognitive function indeed improved with SGA treatment. However, we saw performance deterioration in several cognitive domains at V6, i.e. 24 weeks of FGA treatment.

In contrast to our main finding based on the whole study population, in which we did neither observe a statistically significant difference between the two treatment strategies in CGI-S score nor in PANSS total score (Gründer et al., 2016), such difference was observed in the subgroup reported here. In this subgroup, patients treated with SGAs showed significantly lower scores of PANSS total, PANSS positive, PANSS negative as well as CGI-S at the last visit. The very low PANSS and CGI-S Scores at V6 in this subgroup indicate that only patients with a clear clinical improvement were able to fulfill the study protocol und thus to accomplish all three neurocognitive test sessions. This has to be considered as selection bias, which is difficult to avoid in a longitudinal therapeutic study where a lack of treatment response represents a predefined termination criterion.

However, despite this bias, the performance deterioration in several cognitive domains after 24 weeks of treatment with FGAs remains one of the most noteworthy findings in our study. This stands in contrast with findings of the CATIE trial, where treatment with the FGA perphenazine for several months slightly improved cognitive performance. This difference in outcome cannot be attributed to the medication dosage – we observed cognitive deterioration under a low to moderate FGA medication, i.e. 3.8 mg/day haloperidol and 6.3 mg/day flupentixol, corresponding to 0.5 and 1.1 DDD, respectively (Leucht et al., 2016), as compared to 21.5 mg/d perphenazine in the CATIE trial, corresponding to nearly the same effective dose, 0.7 DDD. Interestingly, at the same time the mean medication dosage of the SGAs in our study (aripiprazole 12.6 mg/d (0.9 DDD), olanzapine 15.5 mg/day (1.6 DDD), quetiapine 470.3 mg/day (1.1 DDD); all SGAs: 1.1 DDD) was somewhat below the dosages used in the CATIE trail (olanzapine: 21.0 mg/d (2.1 DDD), quetiapine 566.3 mg/d (1.42 DDD), risperidone, 4.1 mg/d (0.82 DDD) and ziprasidone (121.9 mg/d (1.52 DDD). Lower dosages may have been partly responsible for the cognitive improvement described above.

Nevertheless, the present NeSSy study is not directly comparable to the CATIE trial, among other aspects because of our use of flupentixol, which is not approved in North America. Despite its traditional classification as a FGA, the pleotropic action of flupentixol, which acts as a powerful antagonist of D_1, D_2 and D_3 dopamine and 5-HT2A receptors (Reimold et al., 2007; Benkert, 2017), indicates an in vivo binding profile lying between typical and atypical antipsychotics. This may account for it relatively minor or even beneficial (Ruhrmann et al., 2007) effects on cognition. Indeed, examination of the test performance specifically in the flupentixol group in our study revealed a significant deterioration solely for the parameter semantic verbal fluency after one minute concerning the achievement in visit 4 (13.0 $\pm$ 6.4), which was significantly worse ($p = 0.016$) than at baseline (16.8 $\pm$ 5.6). Performance impairments were not observed for any other cognitive parameter compared to baseline. Then again, in the flupentixol group we observed a significant executive function improvement in the first six weeks of treatment as well as an improvement in working memory performance in both observation periods. None of those performance enhancements were found in the haloperidol group. This observation indicates that the main part of cognitive decline observed under FGAś, could be attributed to the predominant dopaminergic antagonism without an accompanying action on 5HT receptors. Similarly to flupentixol, the high affinity of perphenazine for serotonin 5HT2A receptors (Gunes et al., 2007; Leysen et al., 1993) may have accounted for the sparing of cognition noted in the CATIE trial. Accordingly, a systematic review of neuroimaging findings showed that high affine, virtually isolated D_2 receptor blockade induces most pronounced prefrontal activation decrease while weaker D_2 antagonists with coincidently appreciable 5-HT_{2A} antagonism were found to rather preserve or increase activation of the prefrontal cortex (Liemburg et al., 2012).

The discussed findings are also interesting in the context of the ongoing demand for a new classification of psychotropic drugs (Uchida, 2018), emphasizing the importance of considering the precise mode of action when prescribing antipsychotics rather than the traditional classification. Indeed, the new version of the NbN acknowledges the difference between haloperidol and flupentixol, which were both part of the FGA group in our study. Regarding our SGA strategy group, aripiprazole shows a considerably different pharmacological profile than olanzapine and quetiapine. Due to its D_2 and 5-HT_{1A} partial agonism aripiprazole is sometimes called a dopamine-serotonin system stabilizer. It is supposed to be able to act as an antagonist in pathways where an abundance of dopamine is producing psychosis, or to stimulate receptors as an agonist at sites with low dopaminergic tone (Khanna et al., 2014). Although several previous studies reported some superiority of aripiprazole over other atypical antipsychotics regarding cognitive effects (Kim et al., 2009; Riedel et al., 2010b) a recent meta-analysis could not confirm this (Khanna et al., 2014). Our findings are in line with this report in that similar beneficial, but not significantly disparate effects of the three SGA substances were revealed in our study.

One further noteworthy finding of our study is the different time course of the cognitive performance changes in the two treatment strategies. The FGA and SGA treatment groups both showed similar initial improvements in the TMT tasks upon short-term treatment. In this initial

treatment period performance deterioration was only observed in one cognitive domain (verbal fluency) in the FGA group. With longer treatment duration the FGA groups deteriorated in several cognitive domains (executive functions, verbal memory, semantic fluency), while the SGA groups did not. Although we could not demonstrate a correlation between changes in cognitive performance and changes in psychopathology, the initial cognitive improvement may have followed the general symptom and well-being improvement, as has already been demonstrated previously, particularly in relation to negative symptoms (Anda et al., 2016; Bora and Murray, 2014; Riedel et al., 2010a). In view of the observed deterioration in the FGA group during the longer treatment period, the question arises, might an early dose reduction have mitigated against the delayed negative effects of FGAs on cognition? This has indeed been reported previously (Kawai et al., 2006; Takeuchi et al., 2013), and others report that reduction or discontinuation of antipsychotic treatment was associated with better functional remission rates after seven years (Wunderink et al., 2013). Furthermore, Harrow et al. (2014, 2017) observed fewer psychotic symptoms, less hospital admissions and better work performance in the group without continuous prescription of antipsychotics during 20 years. Similarly, Albert et al. (2018) reported that patients who discontinued antipsychotic medication improved significantly more in global cognition than those who remained on antipsychotic medication during the course of the 3.5 years follow-up from the naturalistic OPUS II trial. On the other hand, a 10 years long-term observation of patients with an early treatment discontinuation from antipsychotic maintenance following first-episode schizophrenia revealed a poorer outcome compared to patients in the maintenance treatment group (Hui et al., 2018). Taken together, these findings call for rethinking of the prevalent approach of aiming rigidly for high-dosage and long-term maintenance treatment of schizophrenia patients, even after a substantial decline of acute symptoms.

In this context, the very controversial and nowadays intensively debated hypothesis of the potentially harmful effects of antipsychotic medications on brain structure (Andreasen et al., 2013) and function (Abbott et al., 2013) should be mentioned shortly. One meta-analysis showed that higher daily doses of antipsychotics impaired processing speed in patients with schizophrenia (Knowles et al., 2010). Long term observation of the Northern Finland Birth Cohort 1966 associated higher lifetime cumulative doses of antipsychotics (SGAs and FGAs) with declining verbal learning and memory and generally poorer cognitive performance in middle aged schizophrenia patients (Husa et al., 2014), as likewise seen in other naturalistic, cross-sectional studies (Elie et al., 2010; Hori et al., 2006; Torniainen et al., 2012). Despite the short observation period, our present results draw attention to the potential of certain antipsychotics to have a net negative influence on cognition and potentially also on the progression of disease.

The interpretation of our study results and their extrapolation to some more general conclusions demands a clear statement about the study limitation. The main limitation of our study certainly lies in the small sample size, which is indeed a shortcoming of many randomized clinical trials in schizophrenia patients, despite involvement of multiple study centers. As reported previously (Schulz et al., 2016), most of our eligible patients declined to participate in the study. This could be due to excessive demand placed by the complex study design, but also likely reflects the symptom severity and general distrust in schizophrenia patients. Indeed, many of our included patients dropped out prematurely, and others were unwilling or unable to perform all scheduled examinations. This resultant incompleteness of the data, especially in the domain of cognitive testing, further reduced the statistical power. Further, our lack of correction for multiple testing is in keeping with the exploratory nature of our statistical analysis.

Finally, a categorical limitation arises from the use of the traditional classification in FGAs and SGAs, which was generally accepted at the time point of the study conception and is still widely in use, but appears somewhat outdated in the context of the current demand for improved classification system of psychotropic drugs and implementation of the Neuroscience-based Nomenclature (NbN) (Caraci et al., 2017; Uchida, 2018; Zohar et al., 2015). Indeed, a precise consideration of the pharmacology and mode of action differences between the single substances is indispensable for the correct interpretation of our results.

Despite these limitations, our results should motivate further efforts to define the best possible strategies against cognitive impairments in schizophrenia. Besides identifying the most beneficial and least harmful substances, our findings direct the focus on further investigations on the optimal dosage and treatment duration.

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Trial registration

German Clinical Trials Register DRKS00000304. http://www.drks.de/drks_web/navigate.do?navigationId=trial.HTML&TRIAL_ID=DRKS00000304

Declaration of individual contributions to the manuscript

Authors MH, GG, JC, BM, GJ, UH, ER and JT designed the study and wrote the protocol. Members of NeSSy study group

provided the protocol creation, data collection, literature searches and analyses. Authors MS, TV and JT undertook the statistical analysis, and author TV wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interests

Dr. Gründer has served as a consultant for Allergan (Dublin, Ireland), Boehringer Ingelheim (Ingelheim, Germany), Eli Lilly (Indianapolis, Ind, USA), Janssen-Cilag (Neuss, Germany), Lundbeck (Copenhagen, Denmark), Ono Pharmaceuticals (Osaka, Japan), Otsuka (Chiyoda, Japan), Recordati (Milan, Italy), Roche (Basel, Switzerland), Servier (Paris, France), and Takeda (Osaka, Japan). He has served on the speakers' bureau of Eli Lilly, Janssen Cilag, Neuraxpharm (Langenfeld, Germany), Lundbeck, Otsuka, Recordati, Roche, Servier, and Trommsdorf (Aachen, Germany). He has received grant support from Boehringer Ingelheim and Roche. He is co-founder of Mind and Brain Institute GmbH (Zornheim, Germany) and Brainfoods GmbH (Zornheim, Germany). Dr. Cordes was involved in studies which were sponsored by Boehringer Ingelheim Pharma GmbH, Otsuka Pharmaceutical Europe Ltd., and EnVivo Pharmaceuticals.

Dr. Veselinović, Dr. Scharpenberg, Dr. Heinze, Dr. Mühlbauer, Dr. Juckel, Dr, Habel, Dr. Rüther and Dr. Timm declare no conflicts of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.euroneuro.2019.03.014.

References

Abbott, C.C., Jaramillo, A., Wilcox, C.E., Hamilton, D.A., 2013. Antipsychotic drug effects in schizophrenia: a review of longitudinal FMRI investigations and neural interpretations. Curr. Med. Chem. 20, 428–437.

Albert, N., Randers, L., Allott, K., Jensen, H.D., Melau, M., Hjorthøj, C., Nordentoft, M., n.d, 2018. Cognitive functioning following discontinuation of antipsychotic medication. A naturalistic sub-group analysis from the OPUS II trial. Psychol. Med. 1–10. doi:10.1017/S0033291718001836.

Anda, L., Brønnick, K.S., Johnsen, E., Kroken, R.A., Jørgensen, H., Løberg, E.-M., 2016. The course of neurocognitive changes in acute psychosis: relation to symptomatic improvement. PLoS One 11. doi:10.1371/journal.pone.0167390, e0167390-e0167390.

Andreasen, N.C., Liu, D., Ziebell, S., Vora, A., Ho, B.-C., 2013. Relapse duration, treatment intensity, and brain tissue loss in schizophrenia: a prospective longitudinal MRI study. Am. J. Psychiatry 170, 609–615. doi:10.1176/appi.ajp.2013.12050674.

Andreasen, N.C., Pressler, M., Nopoulos, P., Miller, D., Ho, B.-C., 2010. Antipsychotic dose equivalents and dose-years: a standardized method for comparing exposure to different drugs. Biol. Psychiatry 67, 255–262. doi:10.1016/j.biopsych.2009.08.040.

Aschenbrenner, S., Tucha, O., Lange, K.W., 2000. Regensburger Wortflüssigkeitstest (RWT). Hogrefe Verlag, Göttingen.

Barch, D.M., Bustillo, J., Gaebel, W., Gur, R., Heckers, S., Malaspina, D., Owen, M.J., Schultz, S., Tandon, R., Tsuang, M., Van Os, J., Carpenter, W., 2013. Logic and justification for dimensional assessment of symptoms and related clinical phenomena in psychosis: relevance to DSM-5. Schizophr. Res. doi:10.1016/j.schres.2013.04.027.

Bartels, C., Wegrzyn, M., Wiedl, A., Ackermann, V., Ehrenreich, H., 2010. Practice effects in healthy adults: a longitudinal study on frequent repetitive cognitive testing. BMC Neurosci. 11, 118. doi:10.1186/1471-2202-11-118.

Beglinger, L.J., Gaydos, B., Tangphao-Daniels, O., Duff, K., Kareken, D.A., Crawford, J., Fastenau, P.S., Siemers, E.R., 2005. Practice effects and the use of alternate forms in serial neuropsychological testing. Arch. Clin. Neuropsychol. 20 (4), 517–529.

Benkert, O., 2017. Flupentixol. In: Benkert, O., Hippius, H. (Eds.), Kompendium Der Psychiatrischen Pharmakotherapie. Springer, pp. 401–405.

Bird, C.M., Papadopoulou, K., Ricciardelli, P., Rossor, M.N., Cipolotti, L., 2004. Monitoring cognitive changes: psychometric properties of six cognitive tests. Br. J. Clin. Psychol. 43, 197–210. doi:10.1348/014466504323088051.

Bora, E., Murray, R.M., 2014. Meta-analysis of cognitive deficits in ultra-high risk to psychosis and first-episode psychosis: do the cognitive deficits progress over, or after, the onset of psychosis? Schizophr. Bull. 40, 744–755. doi:10.1093/schbul/sbt085.

Bowie, C.R., Harvey, P.D., 2005. Cognition in schizophrenia: impairments, determinants, and functional importance. Psychiatr. Clin. N. Am. 28, 613–633. https://doi.org/10.1016/j.psc.2005.05.004.

Caraci, F., Enna, S.J., Zohar, J., Racagni, G., Zalsman, G., van den Brink, W., Kasper, S., Koob, G.F., Pariante, C.M., Piazza, P.V., Yamada, K., Spedding, M., Drago, F., 2017. A new nomenclature for classifying psychotropic drugs. Br. J. Clin. Pharmacol. 83, 1614–1616. doi:10.1111/bcp.13302.

Caroff, S.N., Davis, V.G., Miller, D.D., Davis, S.M., Rosenheck, R.A., McEvoy, J.P., Campbell, E.C., Saltz, B.L., Riggio, S., Chakos, M.H., Swartz, M.S., Keefe, R.S., Stroup, T.S., Lieberman, J.A.CATIE Investigators, 2011. Treatment outcomes of patients with tardive dyskinesia and chronic schizophrenia. J. Clin. Psychiatry 72 (3), 295–303. doi:10.4088/JCP.09m05793yel.

Collie, A., Maruff, P., Darby, D.G., McStephen, M., 2003. The effects of practice on the cognitive test performance of neurologically normal individuals assessed at brief test-retest intervals. J. Int. Neuropsychol. Soc. 9, 419–428. doi:10.1017/S1355617703930074.

Corrigan, J.D., Hinkeldey, N.S., 1987. Relationships between parts A and B of the trail making test. J. Clin. Psychol. 43, 402–409.

Desamericq, G., Schurhoff, F., Meary, A., Szoke, A., Macquin-Mavier, I., Bachoud-Levi, A.C., Maison, P., 2014. Long-term neurocognitive effects of antipsychotics in schizophrenia: a network meta-analysis. Eur. J. Clin. Pharmacol. 70, 127–134. doi:10.1007/s00228-013-1600-y.

Donohoe, G., Owens, N., O'Donnell, C., Burke, T., Moore, L., Tobin, A., O'Callaghan, E., 2001. Predictors of compliance with neuroleptic medication among inpatients with schizophrenia: a discriminant function analysis. Eur. Psychiatry 16, 293–298.

Elie, D., Poirier, M., Chianetta, J., Durand, M., Gregoire, C., Grignon, S., 2010. Cognitive effects of antipsychotic dosage and polypharmacy: a study with the BACS in patients with schizophrenia and schizoaffective disorder. J. Psychopharmacol. 24, 1037–1044. doi:10.1177/0269881108100777.

Galletly, C.A., Clark, C.R., MacFarlane, A.C., 2000. Treating cognitive dysfunction in patients with schizophrenia. J. Psychiatry Neurosci. 25, 117–124.

Giovagnoli, A.R., Del Pesce, M., Mascheroni, S., Simoncelli, M., Laiacona, M., Capitani, E., 1996. Trail making test: normative

values from 287 normal adult controls. Ital. J. Neurol. Sci. 17, 305–309.

Gold, J.M., Carpenter, C., Randolph, C., Goldberg, T.E., Weinberger, D.R., 1997. Auditory working memory and Wisconsin card sorting test performance in schizophrenia. Arch. Gen. Psychiatry 54, 159–165. doi:10.1001/archpsyc.1997.01830140071013.

Gründer, G., Heinze, M., Cordes, J., Mühlbauer, B., Juckel, G., Schulz, C., Rüther, E., Timm, J., 2016. Effects of first-generation antipsychotics versus second-generation antipsychotics on quality of life in schizophrenia: a double-blind, randomised study. Lancet Psychiatry 3, 717–729. doi:10.1016/S2215-0366(16)00085-7.

Green, M.F., Kern, R.S., Heaton, R.K., 2004. Longitudinal studies of cognition and functional outcome in schizophrenia: implications for MATRICS. Schizophr. Res. 72, 41–51. doi:10.1016/j.schres.2004.09.009.

Gunes, A., Scordo, M.G., Jaanson, P., Dahl, M.-L., 2007. Serotonin and dopamine receptor gene polymorphisms and the risk of extrapyramidal side effects in perphenazine-treated schizophrenic patients. Psychopharmacology (Berl) 190, 479–484. doi:10.1007/s00213-006-0622-x.

Guy, W.(U.S.)., N.I. of M.H., Branch., P.R., Program., E.C.D.E., 1976. ECDEU Assessment Manual for Psychopharmacology. U.S. Dept. of Health, Education, and Welfare, Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration, National Institute of Mental Health, Psychopharmacology Research Branch, Division of Extramural Research Programs, Rockville, Md.

Hagger, C., Buckley, P., Kenny, J.T., Friedman, L., Ubogy, D., Meltzer, H.Y., 1993. Improvement in cognitive functions and psychiatric symptoms in treatment-refractory schizophrenic patients receiving clozapine. Biol. Psychiatry 34, 702–712.

Harvey, P.D., Keefe, R.S., 2001. Studies of cognitive change in patients with schizophrenia following novel antipsychotic treatment. Am. J. Psychiatry 158, 176–184. doi:10.1176/appi.ajp.158.2.176.

Harrow, M., Jobe, T.H., Faull, R.N., 2014. Does treatment of schizophrenia with antipsychotic medications eliminate or reduce psychosis? A 20-year multi-follow-up study. Psychol. Med. 44 (14), 3007–3016. doi:10.1017/S0033291714000610.

Harrow, M., Jobe, T.H., Faull, R.N., Yang, J., 2017. A 20-Year multifollowup longitudinal study assessing whether antipsychotic medications contribute to work functioning in schizophrenia. Psychiatry Res. 265, 267–274. doi:10.1016/j.psychres.2017.06.069.

Hashimoto, N., Toyomaki, A., Honda, M., Miyano, S., Nitta, N., Sawayama, H., Sugawara, Y., Uemura, K., Tsukamoto, N., Koyama, T., Kusumi, I., 2015. Long-term efficacy and tolerability of quetiapine in patients with schizophrenia who switched from other antipsychotics because of inadequate therapeutic response-a prospective open-label study. Ann. Gen. Psychiatry 14, 1. doi:10.1186/s12991-014-0039-6.

Helmstaedtler, von C., Lendt, M., Lux, S., 1990. VLTM: Verbaler Lern- und Merkfähigkeitstest. Manual. Beltz Test GmbH, Göttingen.

Hiemke, C., Baumann, P., Bergemann, N., Conca, A., Dietmaier, O., Egberts, K., Fric, M., Gerlach, M., Greiner, C., Gründer, G., Haen, E., Havemann-Reinecke, U., Jaquenoud Sirot, E., Kirchherr, H., Laux, G., Lutz, U.C., Messer, T., Muller, M.J., Pfuhlmann, B., Rambeck, B., Riederer, P., Schoppek, B., Stingl, J., Uhr, M., Ulrich, S., Waschgler, R., Zernig, G., 2011. AGNP consensus guidelines for therapeutic drug monitoring in psychiatry: update 2011. Pharmacopsychiatry 44, 195–235. doi:10.1055/s-0031-1286287.

Hiemke, C., Bergemann, N., Clement, H.W., Conca, A., Deckert, J., Domschke, K., Eckermann, G., Egberts, K., Gerlach, M., Greiner, C., Gründer, G., Haen, E., Havemann-Reinecke, U., Hefner, G., Helmer, R., Janssen, G., Jaquenoud, E., Laux, G., Messer, T., Mössner, R., Müller, M.J., Paulzen, M., Pfuhlmann, B., Riederer, P., Saria, A., Schoppek, B., Schoretsanitis, G., Schwarz, M., Gracia, M.S., Stegmann, B., Steimer, W., Stingl, J.C., Uhr, M., Ulrich, S., Unterecker, S., Waschgler, R., Zernig, G., Zurek, G., Baumann, P., 2018. Consensus Guidelines for Therapeutic Drug Monitoring in Neuropsychopharmacology: Update 2017. Pharmacopsychiatry 51 (1-02), 9–62. doi:10.1055/s-0043-116492.

Hori, H., Noguchi, H., Hashimoto, R., Nakabayashi, T., Omori, M., Takahashi, S., Tsukue, R., Anami, K., Hirabayashi, N., Harada, S., Saitoh, O., Iwase, M., Kajimoto, O., Takeda, M., Okabe, S., Kunugi, H., 2006. Antipsychotic medication and cognitive function in schizophrenia. Schizophr. Res. 86, 138–146. doi:10.1016/j.schres.2006.05.004.

Hui, C.L.M., Honer, W.G., Lee, E.H.M., Chang, W.C., Chan, S.K.W., Chen, E.S.M., Pang, E.P.F., Lui, S.S.Y., Chung, D.W.S., Yeung, W.S., Ng, R.M.K., Lo, W.T.L., Jones, P.B., Sham, P., Chen, E.Y.H., 2018. Long-term effects of discontinuation from antipsychotic maintenance following first-episode schizophrenia and related disorders: a 10 year follow-up of a randomised, double-blind trial. Lancet Psychiatry 5, 432–442. doi:10.1016/S2215-0366(18)30090-7.

Husa, A.P., Rannikko, I., Moilanen, J., Haapea, M., Murray, G.K., Barnett, J., Jones, P.B., Isohanni, M., Koponen, H., Miettunen, J., Jaaskelainen, E., 2014. Lifetime use of antipsychotic medication and its relation to change of verbal learning and memory in midlife schizophrenia – an observational 9-year follow-up study. Schizophr. Res. 158, 134–141. doi:10.1016/j.schres.2014.06.035.

Jeste, S.D., Patterson, T.L., Palmer, B.W., Dolder, C.R., Goldman, S., Jeste, D.V, 2003. Cognitive predictors of medication adherence among middle-aged and older outpatients with schizophrenia. Schizophr. Res. 63, 49–58.

Johnsen, E., Jorgensen, H.A., Kroken, R.A., Loberg, E.-M., 2013. Neurocognitive effectiveness of quetiapine, olanzapine, risperidone, and ziprasidone: a pragmatic, randomized trial. Eur. Psychiatry 28, 174–184. doi:10.1016/j.eurpsy.2011.10.003.

Jones, P., Rodgers, B., Murray, R., Marmot, M., 1994. Child Development Risk Factors for Adult Schizophrenia in the British 1946 Birth Cohort, 344. Lancet, London, England, pp. 1398–1402.

Jones, P.B., Barnes, T.R.E., Davies, L., Dunn, G., Lloyd, H., Hayhurst, K.P., Murray, R.M., Markwick, A., Lewis, S.W., 2006. Randomized controlled trial of the effect on Quality of Life of second- vs first-generation antipsychotic drugs in schizophrenia: Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS 1). Arch. Gen. Psychiatry 63, 1079–1087. doi:10.1001/archpsyc.63.10.1079.

Joseph, J., Kremen, W.S., Franz, C.E., Glatt, S.J., van de Leemput, J., Chandler, S.D., Tsuang, M.T., Twamley, E.W., 2017. Predictors of current functioning and functional decline in schizophrenia. Schizophr. Res. doi:10.1016/j.schres.2017.01.038.

Kawai, N., Yamakawa, Y., Baba, A., Nemoto, K., Tachikawa, H., Hori, T., Asada, T., Iidaka, T., 2006. High-dose of multiple antipsychotics and cognitive function in schizophrenia: the effect of dose-reduction. Prog. Neuropsychopharmacol. Biol. Psychiatry 30, 1009–1014. doi:10.1016/j.pnpbp.2006.03.013.

Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr. Bull. 13, 261–276.

Keefe, R.S.E., Bilder, R.M., Davis, S.M., Harvey, P.D., Palmer, B.W., Gold, J.M., Meltzer, H.Y., Green, M.F., Capuano, G., Stroup, T.S., McEvoy, J.P., Swartz, M.S., Rosenheck, R.A., Perkins, D.O., Davis, C.E., Hsiao, J.K., Lieberman, J.A., 2007a. Neurocognitive effects of antipsychotic medications in patients with chronic schizophrenia in the CATIE Trial. Arch. Gen. Psychiatry 64, 633–647. doi:10.1001/archpsyc.64.6.633.

Keefe, R.S.E., Bilder, R.M., Harvey, P.D., Davis, S.M., Palmer, B.W., Gold, J.M., Meltzer, H.Y., Green, M.F., Miller, D.D., Canive, J.M., Adler, L.W., Manschreck, T.C., Swartz, M., Rosenheck, R., Perkins, D.O., Walker, T.M., Stroup, T.S., McEvoy, J.P., Lieberman, J.A., 2006. Baseline neurocognitive deficits in the CATIE schizophrenia trial. Neuropsychopharmacology 31, 2033–2046. doi:10.1038/sj.npp.1301072.

Keefe, R.S.E., Harvey, P.D., 2012, Cognitive Impairment in Schizophrenia BT – Novel Antischizophrenia Treatments. In: Geyer, M.A., Gross, G. (Eds.). Springer Berlin Heidelberg, Berlin, Heidelberg, pp. 11–37. doi:10.1007/978-3-642-25758-2_2.

Keefe, R.S.E., Seidman, L.J., Christensen, B.K., Hamer, R.M., Sharma, T., Sitskoorn, M.M., Lewine, R.R.J., Yurgelun-Todd, D.A., Gur, R.C., Tohen, M., Tollefson, G.D., Sanger, T.M., Lieberman, J.A., 2004. Comparative effect of atypical and conventional antipsychotic drugs on neurocognition in first-episode psychosis: a randomized, double-blind trial of olanzapine versus low doses of haloperidol. Am. J. Psychiatry 161, 985–995. doi:10.1176/appi.ajp.161.6.985.

Keefe, R.S.E., Sweeney, J.A., Gu, H., Hamer, R.M., Perkins, D.O., McEvoy, J.P., Lieberman, J.A., 2007b. Effects of olanzapine, quetiapine, and risperidone on neurocognitive function in early psychosis: a randomized, double-blind 52-week comparison. Am. J. Psychiatry 164, 1061–1071. doi:10.1176/ajp.2007.164.7.1061.

Khanna, P., Suo, T., Komossa, K., Ma, H., Rummel-Kluge, C., El-Sayeh, H.G., Leucht, S., Xia, J., 2014. Aripiprazole versus other atypical antipsychotics for schizophrenia. Cochrane Database Syst. Rev. doi:10.1002/14651858.CD006569.pub5, CD006569.

Kim, S.-W., Shin, I.-S., Kim, J.-M., Lee, J.-H., Lee, Y.-H., Yang, S.-J., Yoon, J.-S., 2009. Effectiveness of switching to aripiprazole from atypical antipsychotics in patients with schizophrenia. Clin. Neuropharmacol. 32, 243–249. doi:10.1097/WNF.0b013e31819a68b5.

Knowles, E.E.M., David, A.S., Reichenberg, A., 2010. Processing speed deficits in schizophrenia: reexamining the evidence. Am. J. Psychiatry 167, 828–835. doi:10.1176/appi.ajp.2010.09070937.

Kurtz, M.M., Wexler, B.E., Fujimoto, M., Shagan, D.S., Seltzer, J.C., 2008. Symptoms versus neurocognition as predictors of change in life skills in schizophrenia after outpatient rehabilitation. Schizophr. Res. 102, 303–311. doi:10.1016/j.schres.2008.03.023.

Lehrl, S., Merz, J., Burkhard, G.F.S., 1977. Mehrfachwahl-Wortschatz-Test b (MWT-b)[Multiplechoice vocabulary test]. Erlangen, Ger. Straube.

Leucht, S., Kissling, W., Davis, J.M., 2009. Second-generation antipsychotics for schizophrenia: can we resolve the conflict? Psychol. Med. 39, 1591–1602. doi:10.1017/S0033291709005455.

Leucht, S., Samara, M., Heres, S., Davis, J.M., 2016. Dose equivalents for antipsychotic drugs: the DDD method. Schizophr. Bull. 42, S90–S94. doi:10.1093/schbul/sbv167.

Leysen, J.E., Janssen, P.M., Schotte, A., Luyten, W.H., Megens, A.A., 1993. Interaction of antipsychotic drugs with neurotransmitter receptor sites in vitro and in vivo in relation to pharmacological and clinical effects: role of 5HT2 receptors. Psychopharmacology (Berl) 112, S40–S54.

Lieberman, J.A., Stroup, T.S., McEvoy, J.P., Swartz, M.S., Rosenheck, R.A., Perkins, D.O., Keefe, R.S.E., Davis, S.M., Davis, C.E., Lebowitz, B.D., Severe, J., Hsiao, J.K., 2005. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N. Engl. J. Med. 353, 1209–1223. doi:10.1056/NEJMoa051688.

Liemburg, E.J., Knegtering, H., Klein, H.C., Kortekaas, R., Aleman, A., 2012. Antipsychotic medication and prefrontal cortex activation: a review of neuroimaging findings. Eur. Neuropsychopharmacol. 22, 387–400. doi:10.1016/j.euroneuro.2011.12.008.

McClure, M.M., Bowie, C.R., Patterson, T.L., Heaton, R.K., Weaver, C., Anderson, H., Harvey, P.D., 2007. Correlations of functional capacity and neuropsychological performance in older patients with schizophrenia: evidence for specificity of relationships? Schizophr. Res. 89, 330–338. doi:10.1016/j.schres.2006.07.024.

Meltzer, H.Y., 2015. Pharmacotherapy of cognition in schizophrenia. Curr. Opin. Behav. Sci. 4, 115–121. doi:10.1016/J.COBEHA.2015.04.009.

Minor, K.S., Lysaker, P.H., 2014. Necessary, but not sufficient: links between neurocognition, social cognition, and metacognition in schizophrenia are moderated by disorganized symptoms. Schizophr. Res. 159, 198–204. doi:10.1016/j.schres.2014.08.005.

Mishara, A.L., Goldberg, T.E., 2004. A meta-analysis and critical review of the effects of conventional neuroleptic treatment on cognition in schizophrenia: opening a closed book. Biol. Psychiatry 55, 1013–1022. http://doi.org/10.1016/j.biopsych.2004.01.027.

Molina, V., Taboada, D., Aragues, M., Hernandez, J.A., Sanz-Fuentenebro, J., 2014. Greater clinical and cognitive improvement with clozapine and risperidone associated with a thinner cortex at baseline in first-episode schizophrenia. Schizophr. Res. 158, 223–229. doi:10.1016/j.schres.2014.06.042.

NeSSy study protocol. Dec 5, 2012 [WWW Document], n.d. URL http://www.ukaachen.de/%0Dfileadmin/files/klinik-psychiatrie/Download_Personen/NeSSy_%0DStudy_Protocol_Version_04_20121205.pdf (accessed 4-27-2016).

Nielsen, R.E., Levander, S., Kjaersdam Telleus, G., Jensen, S.O.W., Ostergaard Christensen, T., Leucht, S., 2015. Second-generation antipsychotic effect on cognition in patients with schizophrenia – a meta-analysis of randomized clinical trials. Acta Psychiatr. Scand. 131, 185–196. doi:10.1111/acps.12374.

Nuechterlein, K.H., Dawson, M.E., Gitlin, M., Ventura, J., Goldstein, M.J., Snyder, K.S., Yee, C.M., Mintz, J., 1992. Developmental processes in schizophrenic disorders: longitudinal studies of vulnerability and stress. Schizophr. Bull. 18, 387–425.

Nuechterlein, K.H., Green, M.F., Kern, R.S., Baade, L.E., Barch, D.M., Cohen, J.D., Essock, S., Fenton, W.S., Frese, F.J., Gold, J.M., Goldberg, T., Heaton, R.K., Keefe, R.S.E., Kraemer, H., Mesholam-Gately, R., Seidman, L.J., Stover, E., Weinberger, D.R., Young, A.S., Zalcman, S., Marder, S.R., 2008. The MATRICS consensus cognitive battery, Part 1: test selection, reliability, and validity. Am. J. Psychiatry 165, 203–213. doi:10.1176/appi.ajp.2007.07010042.

Patterson, T.L., Lacro, J., McKibbin, C.L., Moscona, S., Hughs, T., Jeste, D.V, 2002. Medication management ability assessment: results from a performance-based measure in older outpatients with schizophrenia. J. Clin. Psychopharmacol. 22, 11–19.

Rajji, T.K., Miranda, D., Mulsant, B.H., 2014. Cognition, function, and disability in patients with schizophrenia: a review of longitudinal studies. Can. J. Psychiatry 59, 13–17. doi:10.1177/070674371405900104.

Reimold, M., Solbach, C., Noda, S., Schaefer, J.-E., Bartels, M., Beneke, M., Machulla, H.-J., Bares, R., Glaser, T., Wormstall, H., 2007. Occupancy of dopamine D(1), D (2) and serotonin (2A) receptors in schizophrenic patients treated with flupentixol in comparison with risperidone and haloperidol. Psychopharmacology (Berl) 190, 241–249. doi:10.1007/s00213-006-0611-0.

Reitan, R.M., 1958. Validity of the trail making test as an indicator of organic brain damage. Percept. Mot. Skills 8, 271–276. doi:10.2466/PMS.8.7.271-276.

Riedel, M., Schennach-Wolff, R., Musil, R., Dehning, S., Cerovecki, A., Opgen-Rhein, M., Matz, J., Seemuller, F., Obermeier, M., Engel, R.R., Muller, N., Moller, H.-J., Spellmann, I., 2010a. Neurocognition and its influencing factors in the treatment of schizophrenia-effects of aripiprazole, olanzapine, que-

tiapine and risperidone. Hum. Psychopharmacol. 25, 116–125. doi:10.1002/hup.1101.

Riedel, M., Spellmann, I., Schennach-Wolff, R., Musil, R., Dehning, S., Cerovecki, A., Opgen-Rhein, M., Matz, J., Seemuller, F., Obermeier, M., Severus, E., Engel, R.R., Muller, N., Moller, H.-J., 2010b. Effect of aripiprazole on cognition in the treatment of patients with schizophrenia. Pharmacopsychiatry 43, 50–57. doi:10.1055/s-0029-1239539.

Ruhrmann, S., Kissling, W., Lesch, O.-M., Schmauss, M., Seemann, U., Philipp, M., 2007. Efficacy of flupentixol and risperidone in chronic schizophrenia with predominantly negative symptoms. Prog. Neuropsychopharmacol. Biol. Psychiatry 31, 1012–1022. doi:10.1016/j.pnpbp.2007.02.014.

Sanchez-Cubillo, I., Perianez, J.A., Adrover-Roig, D., Rodriguez-Sanchez, J.M., Rios-Lago, M., Tirapu, J., Barcelo, F., 2009. Construct validity of the trail making test: role of task-switching, working memory, inhibition/interference control, and visuomotor abilities. J. Int. Neuropsychol. Soc. 15, 438–450. doi:10.1017/S1355617709090626.

Schlagenhauf, F., Dinges, M., Beck, A., Wustenberg, T., Friedel, E., Dembler, T., Sarkar, R., Wrase, J., Gallinat, J., Juckel, G., Heinz, A., 2010. Switching schizophrenia patients from typical neuroleptics to aripiprazole: effects on working memory dependent functional activation. Schizophr. Res. 118, 189–200. doi:10.1016/j.schres.2010.01.022.

Schulz, C., Timm, J., Cordes, J., Gründer, G., Mühlbauer, B., Rüther, E., Heinze, M., 2016. Patient-oriented randomisation: a new trial design applied in the neuroleptic strategy study. Clin. Trials 13, 251–259. doi:10.1177/1740774516639910.

Schooler, N.R., Kane, J.M., 1982. Research diagnoses for tardive dyskinesia. Arch. Gen. Psychiatry 39 (4), 486–487.

Takeuchi, H., Suzuki, T., Remington, G., Bies, R.R., Abe, T., Graff-Guerrero, A., Watanabe, K., Mimura, M., Uchida, H., 2013. Effects of risperidone and olanzapine dose reduction on cognitive function in stable patients with schizophrenia: an open-label, randomized, controlled, pilot study. Schizophr. Bull. 39, 993–998. doi:10.1093/schbul/sbt090.

Tandon, R., Carpenter, W.T., Davis, J.M., 2007. First- and second-generation antipsychotics: learning from CUtLASS and CATIE. Arch. Gen. Psychiatry doi:10.1001/archpsyc.64.8.977.

Tarlov, A.R., Ware, J.E.J., Greenfield, S., Nelson, E.C., Perrin, E., Zubkoff, M., 1989. The medical outcomes study. An application of methods for monitoring the results of medical care. JAMA 262, 925–930.

Taylor, D., Paton, C., Kapur, S., 2015. The Maudsley Prescribing Guidelines in Psychiatry. John Wiley & Sons.

Torniainen, M., Suvisaari, J., Partonen, T., Castaneda, A.E., Kuha, A., Suokas, J., Perala, J., Saarni, S.I., Lonnqvist, J., Tuulio-Henriksson, A., 2012. Cognitive impairments in schizophrenia and schizoaffective disorder: relationship with clinical characteristics. J. Nerv. Ment. Dis. 200, 316–322. doi:10.1097/NMD.0b013e31824cb359.

Trapp, W., Landgrebe, M., Hoesl, K., Lautenbacher, S., Gallhofer, B., Gunther, W., Hajak, G., 2013. Cognitive remediation improves cognition and good cognitive performance increases time to relapse-results of a 5 year catamnestic study in schizophrenia patients. BMC Psychiatry 13, 184. doi:10.1186/1471-244X-13-184.

Uchida, H., 2018. Neuroscience-based nomenclature: what is it, why is it needed, and what comes next? Psychiatry Clin. Neurosci. 72, 50–51. doi:10.1111/pcn.12615.

Vazzana, R., Bandinelli, S., Lauretani, F., Volpato, S., Lauretani, F., Di Iorio, A., Abate, M., Corsi, A.M., Milaneschi, Y., Guralnik, J.M., Ferrucci, L., 2010. Trail Making Test predicts physical impairment and mortality in older persons. J. Am. Geriatr. Soc. 58 (4), 719–723. doi:10.1111/j.1532-5415.2010.02780.x.

van der Gaag, M., Hoffman, T., Remijsen, M., Hijman, R., de Haan, L., van Meijel, B., van Harten, P.N., Valmaggia, L., de Hert, M., Cuijpers, A., Wiersma, D., 2006. The five-factor model of the Positive and Negative Syndrome Scale II: a ten-fold cross-validation of a revised model. Schizophr. Res. 85 (1-3), 280–287.

Woodward, N.D., Purdon, S.E., Meltzer, H.Y., Zald, D.H., 2005. A meta-analysis of neuropsychological change to clozapine, olanzapine, quetiapine, and risperidone in schizophrenia. Int. J. Neuropsychopharmacol. 8, 457–472. doi:10.1017/S146114570500516X.

Wunderink, L., Nieboer, R.M., Wiersma, D., Sytema, S., Nienhuis, F.J., 2013. Recovery in remitted first-episode psychosis at 7 years of follow-up of an early dose reduction/discontinuation or maintenance treatment strategy: long-term follow-up of a 2-year randomized clinical trial. JAMA Psychiatry 70 (9), 913–920. doi:10.1001/jamapsychiatry.2013.19.

Zhang, J.-P., Gallego, J.A., Robinson, D.G., Malhotra, A.K., Kane, J.M., Correll, C.U., 2013. Efficacy and safety of individual second-generation vs. first-generation antipsychotics in first-episode psychosis: a systematic review and meta-analysis. Int. J. Neuropsychopharmacol. 16, 1205–1218. doi:10.1017/S1461145712001277.

Zohar, J., Kasper, S., 2016. Neuroscience-based nomenclature (NbN): a call for action. World J. Biol. Psychiatry 17, 318–320. doi:10.1080/15622975.2016.1193626.

Zohar, J., Nutt, D.J., Kupfer, D.J., Moller, H.-J., Yamawaki, S., Spedding, M., Stahl, S.M., 2014. A proposal for an updated neuropsychopharmacological nomenclature. Eur. Neuropsychopharmacol. 24, 1005–1014. doi:10.1016/j.euroneuro.2013.08.004.

Zohar, J., Stahl, S., Moller, H.-J., Blier, P., Kupfer, D., Yamawaki, S., Uchida, H., Spedding, M., Goodwin, G.M., Nutt, D., 2015. A review of the current nomenclature for psychotropic agents and an introduction to the neuroscience-based Nomenclature. Eur. Neuropsychopharmacol. 25, 2318–2325. doi:10.1016/j.euroneuro.2015.08.019.