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# Meta-analysis of cognitive performance in drug-naïve patients with schizophrenia

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ABSTRACT

Cognitive deficits represent a significant characteristic of schizophrenia. However, a majority of the clinical studies have been conducted in antipsychotic drug treated patients. Thus, it remains unclear if significant cognitive impairments exist in the absence of medication. This is the first meta-analysis of cognitive findings in drug-naïve patients with schizophrenia. Cognitive data from 23 studies encompassing 1106 patients and 1385 controls published from 1992 to 2013 were included. Tests were to a large extent ordered in cognitive domains according to the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) battery. Analysis was performed with STATA using the random-effects model and heterogeneity as well as Egger's publication bias was assessed. Overall the results show that patients performed worse than healthy controls in all cognitive domains with medium to large effect sizes. Verbal memory, speed of processing and working memory were three of the domains with the greatest impairments. The pattern of results is in line with previous meta-analytic findings in antipsychotic treated patients. The present meta-analysis confirms the existence of significant cognitive impairments at the early stage of the illness in the absence of antipsychotic medication.



## 1. Introduction

Kraepelin coined the concept "dementia praecox" in 1896. On the basis of clinical observations, he had thereby captured the negative symptoms of schizophrenia and most likely also some of the cognitive deficits. Half a century later, the evolvement of neuropsychology allowed for systematic testing of his clinical observations, and cognitive deficits have since then been convincingly demonstrated in schizophrenia and confirmed by meta-analyses (Heinrichs and Zakzanis, 1998; Mesholam-Gately et al., 2009; Schaefer et al., 2013).

However, since neuroleptic drugs were introduced in the early 1950s a majority of the studies have been conducted in drug treated patients. In healthy subjects, administration of antipsychotic medication has generally been found to have a negative impact on cognitive performance in domains such as speed of processing and attention (Ramaekers et al., 1999; Saeedi et al., 2006; Vernaleken et al., 2006; Veselinovic et al., 2013). Importantly, antipsychotic drugs occupy the D2-dopamine receptor (Carlsson and Lindqvist, 1963; Farde et al., 1992). The role of this receptor subtype specifically in cognitive function has been confirmed in studies employing Positron Emission Tomography (PET), showing that poor cognitive performance in several domains is associated to low D2-receptor binding (Volkow et al., 1998; Bäckman, et al., 2000; Cropley et al., 2006; Takahashi et al., 2007; Cervenka et al., 2008). In addition, antipsychotic drugs commonly affect also other neurotransmitter systems of importance for cognitive function, such as the cholinergic system (Barak, 2009). Thus, it remains unclear if previous observations of cognitive deficits in schizophrenia solely can be attributed to the underlying disorder or to some degree represent an effect of antipsychotic drug treatment.

Until recently, research on cognition in drug-naïve patients with schizophrenia has been hampered by small samples and by the great variety of cognitive tests used. Several of the reports have been imaging studies usually enrolling limited samples (Cleghorn et al., 1989; Andreasen et al., 1992; Buchsbaum et al., 1992; Parellada et al., 1994; Barch et al., 2001; Salgado-Pineda et al., 2003; Jones et al., 2004; Harrison et al., 2006). Although research on drug-naïve high risk to psychosis subjects has shown cognitive impairments even before psychosis onset (Bora and Murray, 2014; Bora et al., 2014) meta-analytic evidence from drug-naïve schizophrenia subjects is lacking.

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However, during the last few years results from several larger studies of drug-naïve patients with schizophrenia have been published (Hill et al., 2004; Chan et al., 2006; Wang et al., 2007; Hu et al., 2011; Andersen et al., 2013; Lu et al., 2012; Zhang et al., 2012; He et al., 2013).

The primary aim of the present meta-analysis was to analyze findings from studies on cognitive deficits in drug-naïve patients with schizophrenia.

## 2. Methods

### 2.1. Literature search

PubMed and PsycInfo were searched using the following syntax: (cognition OR cognitive OR neurocognitive OR neuropsychological OR neuropsychologic OR neurocognition) AND (psychosis OR psychotic OR schizophrenia) AND (drug naïve OR drug-naïve OR never treated OR never-treated OR neuroleptic naïve OR neuroleptic-naïve OR antipsychotic naïve OR antipsychotic-naïve OR never medicated OR never-medicated OR treatment naïve OR treatment-naïve). No time limitation was set. The search was performed on the 1st of November 2012 and gave 272 hits. The abstracts of the 272 articles were read and the 134 articles judged to be relevant to the topic were read in full length.

To be included in the analysis the studies had to meet the following criteria: (a) to include patients with schizophrenia spectrum disorders using DSM-III, DSM-III-R, DSM-IV, ICD-9 or ICD-10 (5 articles were excluded due to this criterion); (b) to have a sample of drug-naïve patients. If a study included both drug-naïve and medicated patients, separate data on the drug-naïve patients had to be available (20 articles excluded); (c) to include cognitive performance (12 articles excluded); (d) to include a healthy control group (16 articles excluded); (e) to tap one of the 7 cognitive domains covered by the Measurement and Treatment Research to Improve Cognition in Schizophrenia MATRICS battery (Kern et al., 2008; Nuechterlein et al., 2008). Articles using cognitive tests not covered by MATRICS were excluded (23 articles excluded); (f) to have cognitive data presented separately and not only as correlates to other measurements (6 articles excluded); (g) if a sample was re-used only the article with the largest number of patients was included (10 excluded). However, if two studies used overlapping samples but examined different cognitive domains with different tests, then both studies were included; (h) only original articles were included, review articles and case reports were excluded (8 articles excluded); (i) only articles written in English were included (3 excluded due to this criterion); (j) if data in an article were incomplete for the present purpose, the authors were asked to provide additional information by e-mail (10 articles excluded due to lack of response).

Following this exclusion procedure 21 articles remained for analysis. Two additional articles were identified after screening the reference lists of the 21 articles. The final number of articles included in the analysis was thereby 23.

### 2.2. Sample

The meta-analysis was based on a total of 1106 patients and 1385 controls. A majority of the patients had the diagnosis of schizophrenia (89.60%), 2.26% were diagnosed with schizoaffective disorder, 1.35% with schizophreniform disorder and 5.15% included mixed samples of schizophrenia, and schizoaffective and schizophreniform disorder. One study (Brickman et al., 2004) included a majority of patients with schizophrenia (18 individuals) but also some individuals diagnosed with bipolar disorder (5 individuals), major depression with psychosis (1 individual) and psychosis not otherwise specified (NOS) (1 individual). With the exception of 3 studies including a total of 43 patients where information was lacking, all included studies had enrolled first episode schizophrenia patients, here defined as patients in their first contact with psychiatry. The sample characteristics are presented in Table 1. Publication year ranged from 1992 to 2013. A detailed description of the sample, including country of study origin, details about duration of untreated psychosis (DUP) and diagnoses, is given in Tables 1 and 2 in the Supplementary data.

**Table 1**
Sample characteristics.

| Characteristic | Patients | | | Controls | | |
|---|---|---|---|---|---|---|
| | N | Mean (SD) | Range | N | Mean (SD) | Range |
| Sample size | 23 | 48.0 | 12–214 | 23 | 60.2 | 12–452 |
| Age | 21 | 27.2 (8.7) | 16–62 | 20 | 27.5 (8.8) | 16–62 |
| % male | 21 | 64.3 | – | 21 | 60.4 | – |
| Education years | 13 | 12.0 (1.3) | 9–14 | 13 | 13.7 (2.0) | 10–16 |
| DUP[a] months | 8 | 27.9 (30.6) | 4.9–55.2 | – | – | – |

[a] Duration of untreated psychosis.

### 2.3. Neurocognitive tests

Cognitive tests were sorted according to five of the seven cognitive domains of the MATRICS battery: verbal memory (VeM) (refers to immediate verbal memory), speed of processing (SoP), working memory (WM), attention (ATT) and visual memory (ViM) (refers to immediate visual memory). The main purpose of the MATRICS battery is to provide an outcome measure for clinical trials of cognition-enhancing drugs for schizophrenia and is the result of a unique consensus process. MATRICS is today the only FDA-approved test battery for measuring cognition in research on schizophrenia, and sets the standard within the field. Our intention was thus to provide a meta-analysis that could serve as basis for future cognition studies in schizophrenia using the MATRICS battery. Thereby, only results from tests used in MATRICS or from tests similar to the tests included in MATRICS were used.

Two cognitive domains had been poorly assessed by the reviewed studies. In MATRICS the domain of reasoning and problem solving is measured by Mazes. This test or any equivalent test had not been used in any of the studies included in the present meta-analysis. Instead, the cognitive domain of executive functioning (ExF) was included in the analysis to partly capture the reasoning and problem solving domain. Moreover, the cognitive domain of social cognition is measured in MATRICS by Mayer–Salovey–Caruso Emotional Intelligence Test: Managing Emotions. This test had also not been used in the reviewed studies and no replacement test was identified. The included tests and outcome measures are listed in Table 2.

### 2.4. Statistical analyses

Meta-analysis was performed with the software STATA, version 12. The analysis was conducted by the STATA Metan command using the random-effects model (DerSimonian and Laird, 1986). Cohen's method was chosen to compute the standardized mean differences (SMD) for performance in the neurocognitive tests (the difference between patients and control group means divided by the pooled standard deviation). A value of 0.20–0.50 corresponds to small effect sizes, 0.50–0.80 to medium and a value over 0.80 to large effect sizes. Tests for which low scores indicate better performance were transformed by adding a minus, so that high scores always correspond to better performance. Similar but not identical tests for the same outcome measure were grouped (e.g. CPT tasks). The same test could be included several times in the analysis but with different and non-overlapping outcome measures.

Heterogeneity was assessed by the $I^2$ statistic describing the percentage of variation across studies due to heterogeneity rather than chance (Higgins and Thompson, 2002; Higgins et al., 2003). A value of 0.25% corresponds to low, 0.50% to moderate and 0.75% to high heterogeneity. The weight that was addressed to each SMD in the calculation of overall SMDs was based on sample size. Publication bias was

**Table 2**
Tests and outcome measures for the domains included in the meta-analysis.

| Domain | Tests and outcome measures |
|---|---|
| Verbal memory | Buschke Selective Reminding Test (BSRT) (outcome measure: total recall) |
| | Serial Verbal Learning Task (outcome measure: total recall) |
| | Hopkins Verbal Learning Test—Revised (HVLT-R) (outcome measure: total recall) |
| | Immediate Memory from Repeatable Battery for the Assessment of Neuropsychological Status (outcome measure: total recall) |
| | Logical Memory Test from Wechsler Memory Scale (WMS) (outcome measure: immediate recall) |
| | California Verbal Learning Test (CVLT) (outcome measure: total recall trials 1–5, list A) |
| Speed of processing | Verbal fluency letter "S" (outcome measure: amount of words) |
| | Verbal fluency animal naming (outcome measure: amount of words) |
| | TMT A (outcome measure: time) |
| | WAIS-R Digit Symbol (outcome measure: nr of digits) |
| Working memory | Letter number span (outcome measure: digits and letters recalled) |
| | Digit span from: WMS or WAIS or WISC-III or WAIS-R (all outcome measure: digits recalled) |
| | Spatial Span WMS—3rd ed. (outcome measure: length) |
| | Spatial Span CANTAB (SSP) (outcome measure: length) |
| | AX CPT (score: d′ long delay) |
| | Paced Auditory Serial Addition Test (outcome measure: nr. correct responses) |
| | CANTAB (SWM, Spatial Working Memory) (outcome measures: strategy, total errors) |
| | Verbal N—back task (2-back) (outcome measure: d′ sensitivity measure) N—back (1-back) (outcome measure: % correct responses) |
| | Sternberg WM task (outcome measure: accuracy %) |
| Attention | CANTAB (RVP, outcome measure: RVP A, mean latency) |
| | Several CPT tests: CPT-IP, CPT-37 version, CPT, Vigilance test, Continuous Attention Test (outcome measure: omission errors, commission errors, A′, d′, hit rate) |
| Visual memory | Rey—Osterrieth Complex Figure (RCFT) (outcome measure: immediate recall) |
| | Figure Recall Test from RBANS (outcome measure: immediate recall) |
| | Pattern Recognition Memory test (PRM) immediate recall (outcome measure: % of correction) |
| | Brief Visuospatial Memory Test Revised (BVMT-R) (outcome measure: total recall) |
| | Visual Reproduction I WMS 3rd (outcome measure: total recall) |
| Executive functioning | CANTAB (IED) (outcome measure: total errors adjusted) |
| | CANTAB (SOC) (outcome measure: problems solved in minimum moves, mean moves) |
| | Tower of London (outcome measure: nr of frames completed) |
| | TMT B (outcome measure: time) |
| | Wisconsin Card Sorting Test (WCST) modified version & WCST 128 & 64 card versions (outcome measure: categories completed, total no. of errors, perseverative errors) |

calculated by the STATA Metabias command using the Egger's test (Egger et al., 1997). This test indicates the presence of asymmetry and bias in the literature, such as exclusion of non-significant studies. Meta-analytic regression was performed using the STATA Metareg command to evaluate the following moderator variables having sufficient data included in the reports: age, education years, gender (male ratio) and publication year. Descriptive statistics for the sample characteristics were calculated with SPSS, version 20.

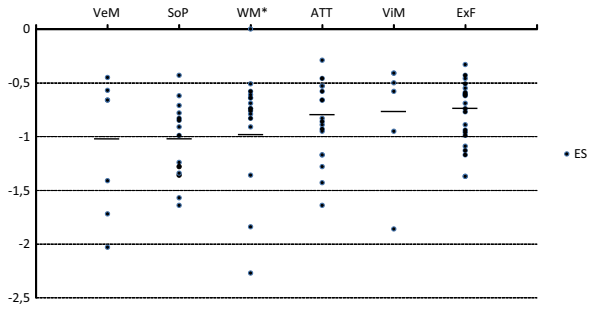



**Fig. 1.** Effect sizes (SMD) for the cognitive domains included in the meta-analysis of drug-naïve patients with schizophrenia each included ES corresponding to one data point (VeM: n = 567, SMD = −1.03 (95% CI = −1.44, −0.63); SoP: n = 361, SMD = −1.03 (95% CI = −1.23, −0.82); WM: n = 375, SMD = −0.97 (95% CI = −1.25, −0.69) (including the outlier Sternberg WM task (outcome: accuracy %) from van Veelen et al. (2011)); ATT: n = 364, SMD = −0.80 (95% CI = −0.95, −0.65); ViM: n = 326, SMD = −0.78 (95% CI = −1.21, −0.34); ExF: n = 529, SMD = −0.74 (95% CI = −0.85, −0.62). *Outlier Sternberg WM task (outcome: accuracy %) from van Veelen et al. (2011) excluded in the figure, SMD = −5.37 (95% CI = −6.51, −4.22).

## 3. Results

Overall the controls outperformed the patients and there were medium to large effect sizes in all cognitive domains. An overview of the results for all domains is given in Fig. 1.

The domains of verbal memory, speed of processing and working memory had the largest effect sizes (Tables 3–5). Each domain is in the following presented separately in the order given by the effect size (Tables 3–8).

For the domain verbal memory (overall SMD = -1.03) (Table 3) the Egger's coefficient bias did not indicate publication bias. Without the two outliers, Hopkins Verbal Learning Test-R and Serial Verbal Learning Task, the heterogeneity dropped to $I^2 = 77.3\%$, $p = 0.001$ (SMD = −0.75, CI = −1.05 to −0.44) but was still high. Moderator analysis was not possible to perform due to insufficient observations.

For the cognitive domain speed of processing (overall SMD = -1.03) (Table 4) the Egger's coefficient bias did not indicate the presence of publication bias. Heterogeneity was moderate. None of the moderating variables; age, gender, education and publication year was significant, but there was a trend for age ($p = 0.064$) indicating that lower age corresponded to smaller ESs.

The cognitive domain of working memory showed an overall effect size of SMD = −0.97 (Table 5). Again, the heterogeneity in this domain was high but dropped to moderate levels when excluding the outlier Sternberg WM task $I^2 = 59.1\%$, $p = 0.001$ (SMD = −0.79, CI = −0.96 to −0.61). The Egger's coefficient bias was −4.804 ($P > |t| = 0.009$) and indicates the presence of asymmetry and publication bias for this domain. Moderating variables, age [$t(12) = 3.50$, $p = 0.010$], gender [$t(12) = -7.90$, $p < 0.001$] and publication year [$t(12) = 6.53$, $p < 0.001$], were significant for this cognitive domain. ESs increased with the percentage of males in the patient group and decreased with the recency of publication year and lower age of the patient group.

**Table 3**
Tests and effect sizes for the cognitive domain: verbal memory.
*Note.* nES = number of effect sizes; k = number of studies; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; WMS = Wechsler Memory Scale; outcome measure for all Verbal Memory tests = immediate recall.

| Test | SMD (95% CI) | N pat. | N contr. | % weight | nES | k | *z* | *p* |
|---|---|---|---|---|---|---|---|---|
| Buschke Selective Reminding Test | –0.57 (–0.98, –0.16) | 48 | 48 | 14.33 | 1 | 1 | 2.73 | 0.006 |
| Serial Verbal Learning Task | –1.72 (–2.42, –1.02) | 29 | 17 | 11.24 | 1 | 1 | 4.82 | <.001 |
| Hopkins Verbal Learning Test | –2.03 (–2.49, –1.57) | 56 | 56 | 13.83 | 1 | 1 | 8.70 | <.001 |
| Immediate Memory from RBANS | –0.66 (–0.88, –0.44) | 214 | 132 | 15.93 | 1 | 1 | 5.81 | <.001 |
| California Verbal Learning Test | –0.66 (–1.02, –0.31) | 62 | 67 | 14.85 | 1 | 1 | 3.65 | <.001 |
| Logical Memory Test from WMS | –0.92 (–1.86, 0.02) | 158 | 132 | 29.82 | 2 | 2 | 1.93 | 0.054 |
| **Overall ($I^2$ = 88.4%, $p$ = 0.00)** | **–1.03 (–1.44, –0.63)** | **567** | **452** | **100.00** | **7** | **7** | **4.96** | **<.001** |

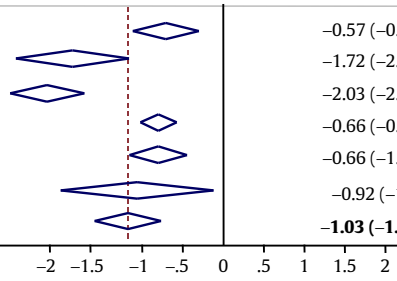



**Table 4**
Tests and effect sizes for the cognitive domain: speed of processing.
*Note.* nES = number of effect sizes; k = number of studies.

| Test, outcome measure | SMD (95% CI) | N pat. | N contr. | % weight | nES | k | *z* | *p* |
|---|---|---|---|---|---|---|---|---|
| WAIS–R Digit Symbol, no.digits | –1.41 (–1.71, –1.12) | 125 | 105 | 14.85 | 2 | 2 | 9.54 | <.001 |
| Verbal fluency, amount words | –1.17 (–1.53, –0.81) | 232 | 214 | 34.43 | 5 | 4 | 6.32 | <.001 |
| TMT A, time | –0.81 (–1.02, –0.59) | 361 | 311 | 50.72 | 7 | 7 | 7.23 | <.001 |
| **Overall ($I^2$ = 66.5%, $p$ = 0.000)** | **–1.03 (–1.23, –0.82)** | **361** | **311** | **100.00** | **14** | **7** | **9.91** | **<.001** |

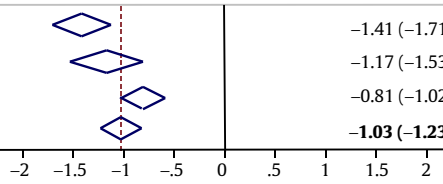



**Table 5**
Tests and effect sizes for the cognitive domain: working memory.
*Note.* nES = number of effect sizes; k = number of studies; WMS = Wechsler Memory Scale; PASAT = Paced Auditory Serial Addition Test.

| Test, outcome measure | SMD (95% CI) | N pat. | N contr. | % weight | nES | k | *z* | *p* |
|---|---|---|---|---|---|---|---|---|
| Letter Number Span, digits & letters recalled | –0.51 (–0.86, –0.17) | 78 | 60 | 6.66 | 1 | 1 | 2.94 | 0.003 |
| Digit Span from WMS/WAIS, digits recalled | –0.88 (–1.23, –0.54) | 189 | 201 | 29.75 | 5 | 4 | 5.05 | <.001 |
| Spatial Span, WMS/SSP, outcome: length | –0.76 (–0.98, –0.53) | 160 | 160 | 19.36 | 3 | 2 | 6.53 | <.001 |
| AX CPT (score: d′ long delay) | –1.36 (–1.79, –0.92) | 42 | 61 | 6.28 | 1 | 1 | 6.11 | <.001 |
| PASAT, correct responses | –0.58 (–0.96, –0.20) | 56 | 56 | 6.56 | 1 | 1 | 3.00 | 0.003 |
| CANTAB, SWM, strategy | –0.76 (–1.18, –0.35) | 48 | 48 | 6.37 | 1 | 1 | 3.61 | <.001 |
| CANTAB, SWM, total errors | –0.74 (–1.15, –0.32) | 48 | 48 | 6.37 | 1 | 1 | 3.49 | <.001 |
| N–back task (2–back, 1–back), outcome: d′ | –0.32 (–0.95, 0.31) | 46 | 70 | 11.69 | 2 | 1 | 0.99 | 0.322 |
| N–back, 1–back, % correct responses | –2.27 (–3.32, –1.23) | 12 | 12 | 3.67 | 1 | 1 | 4.27 | <.001 |
| Sternberg WM task, accuracy % | –5.37 (–6.51, –4.22) | 23 | 33 | 3.34 | 1 | 1 | 9.20 | <.001 |
| **Overall ($I^2$ = 83.8%, $p$ = 0.000)** | **–0.97 (–1.25, –0.69)** | **375** | **411** | **100.00** | **17** | **10** | **7.06** | **<.001** |

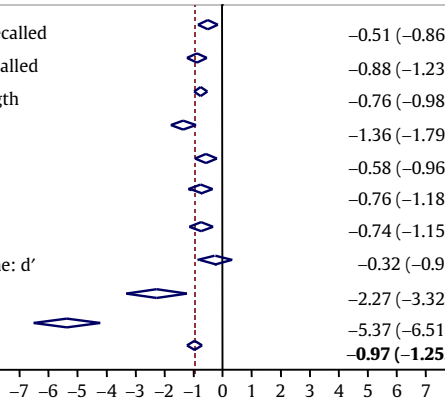



**Table 6**
Tests and effect sizes for the cognitive domain: attention.
*Note.* nES = number of effect sizes; k = number of studies.

| Test, outcome measure | SMD (95% CI) | N pat. | N contr. | % weight | nES | k | *z* | *p* |
|---|---|---|---|---|---|---|---|---|
| CANTAB RVP A | –1.09 (–1.31, –0.86) | 181 | 178 | 25.27 | 4 | 4 | 9.57 | <.001 |
| CANTAB RVP mean latency | –0.74 (–1.02, –0.46) | 108 | 105 | 14.43 | 2 | 2 | 5.22 | <.001 |
| CPT versions omission errors | –0.93 (–1.75, –0.11) | 37 | 57 | 8.14 | 2 | 2 | 2.23 | 0.026 |
| CPT versions comission errors | –0.66 (–1.52, 0.19) | 37 | 57 | 8.41 | 2 | 2 | 1.52 | 0.13 |
| CPT versions d′ | –1.10 (–2.06, –0.14) | 29 | 33 | 6.14 | 2 | 2 | 2.26 | 0.24 |
| CPT versions A′ | –0.52 (–0.71, –0.32) | 136 | 496 | 17.7 | 2 | 2 | 5.25 | <.001 |
| CPT versions hit rate | –0.70 (–0.89, –0.51) | 146 | 500 | 19.91 | 3 | 2 | 7.16 | <.001 |
| **Overall ($I^2$ = 44.3%, $p$ = 0.026)** | **–0.80 (–0.95, –0.65)** | **364** | **731** | **100.00** | **17** | **9** | **11.51** | **<.001** |

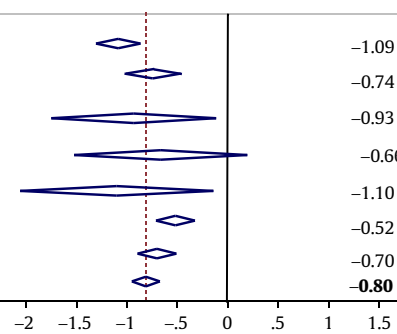


**Table 7**
Tests and effect sizes for the cognitive domain: visual memory.
*Note.* nES = number of effect sizes; k = number of studies; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; WMS = Wechsler Memory Scale; BVMT-R = Brief Visuospatial Memory Test Revised. Most tests have immediate recall as outcome measure. The exception is the Pattern Recognition Memory test having % of correction as outcome.

| Test, outcome measure | SMD (95% CI) | N pat. | N contr. | % weight | nES | k | *z* | *p* |
|---|---|---|---|---|---|---|---|---|
| Rey–Osterrieth Complex Figure | −0.58 (−0.99, −0.17) | 48 | 48 | 16.83 | 1 | 1 | 2.79 | 0.005 |
| Figure Recall Test, RBANS | −0.41 (−0.75, −0.07) | 78 | 60 | 17.63 | 1 | 1 | 2.35 | 0.019 |
| Pattern Recognition Memory test | −0.41 (−0.74, −0.09) | 80 | 72 | 17.83 | 1 | 1 | 2.52 | 0.012 |
| BVMT–R | −1.86 (−2.31, −1.42) | 56 | 56 | 16.38 | 1 | 1 | 8.21 | <.001 |
| Visual reproduction, WMS 3rd | −0.74 (−1.19, −0.30) | 64 | 88 | 31.32 | 2 | 2 | 3.27 | 0.001 |
| **Overall $I^2$ = 85.3%, *p* = 0.000)** | **−0.78 (−1.21, −0.34)** | **326** | **324** | **100.00** | **6** | **6** | **3.50** | **<.001** |

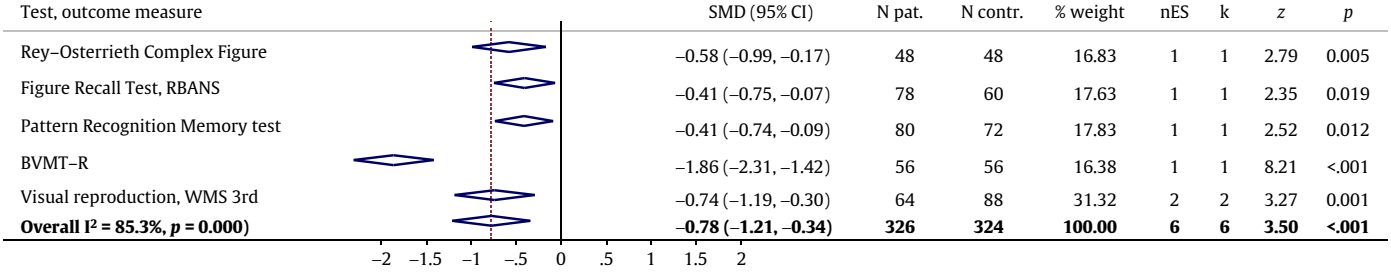
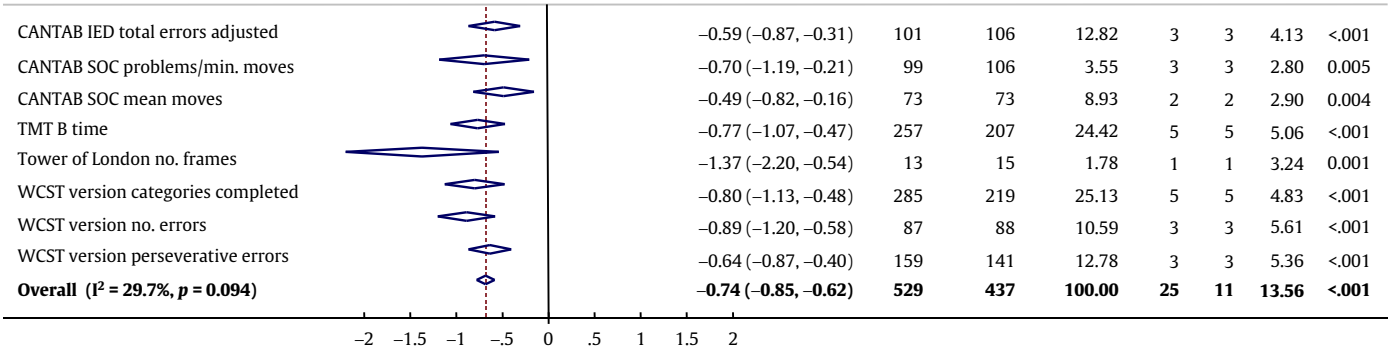



**Table 8**
Tests and effect sizes for the cognitive domain: executive functioning.
*Note.* nES = number of effect sizes; k = number of studies; WCST = Wisconsin Card Sorting Test.

| Test, outcome measure | SMD (95% CI) | N pat. | N contr. | % weight | nES | k | *z* | *p* |
|---|---|---|---|---|---|---|---|---|
| CANTAB IED total errors adjusted | −0.59 (−0.87, −0.31) | 101 | 106 | 12.82 | 3 | 3 | 4.13 | <.001 |
| CANTAB SOC problems/min. moves | −0.70 (−1.19, −0.21) | 99 | 106 | 3.55 | 3 | 3 | 2.80 | 0.005 |
| CANTAB SOC mean moves | −0.49 (−0.82, −0.16) | 73 | 73 | 8.93 | 2 | 2 | 2.90 | 0.004 |
| TMT B time | −0.77 (−1.07, −0.47) | 257 | 207 | 24.42 | 5 | 5 | 5.06 | <.001 |
| Tower of London no. frames | −1.37 (−2.20, −0.54) | 13 | 15 | 1.78 | 1 | 1 | 3.24 | 0.001 |
| WCST version categories completed | −0.80 (−1.13, −0.48) | 285 | 219 | 25.13 | 5 | 5 | 4.83 | <.001 |
| WCST version no. errors | −0.89 (−1.20, −0.58) | 87 | 88 | 10.59 | 3 | 3 | 5.61 | <.001 |
| WCST version perseverative errors | −0.64 (−0.87, −0.40) | 159 | 141 | 12.78 | 3 | 3 | 5.36 | <.001 |
| **Overall ($I^2$ = 29.7%, *p* = 0.094)** | **−0.74 (−0.85, −0.62)** | **529** | **437** | **100.00** | **25** | **11** | **13.56** | **<.001** |




The cognitive domain attention showed an overall effect size of SMD = −0.80 (Table 6). Heterogeneity was low ($I^2$ = 44.3%, $p$ = 0.02). The Egger's coefficient bias was not significant which indicates absence of publication bias. None of the moderating variables, age, gender, education and publication year, was significant for this domain.

For the cognitive domain of visual memory, the overall effect size was SMD = −0.78 (Table 7). When excluding the outlier Brief Visuospatial Memory Test—Revised the heterogeneity fell to low levels $I^2$ = 2.9%, $p$ = 0.390 (SMD = −0.53, CI = −0.71 to −0.35). The Egger's coefficient bias did not indicate the presence of publication bias. Due to insufficient number of observations it was not possible to perform a moderator analysis.

The overall effect size for the cognitive domain executive functioning was SMD = −0.74 (Table 8). Heterogeneity was low ($I^2$ = 29.7%, p = 0.094). The Egger's coefficient bias did not indicate the presence of publication bias and none of the moderating variables, age, gender, education and publication year, was significant for this cognitive domain.

## 4. Discussion

The present meta-analysis on cognitive performance is the first conducted on solely antipsychotic drug-naïve patients with schizophrenia. Overall, patients performed worse than healthy control subjects across all cognitive domains. The effect sizes were medium to large, and largest for verbal memory, speed of processing and working memory. Both the magnitude of differences and the pattern with pronounced deficits in verbal memory and speed of processing relative to other cognitive domains are in line with previous meta-analyses on studies where most patients were medicated and had been ill for several years (Saykin et al., 1991; Heinrichs and Zakzanis, 1998; Aleman et al., 1999; Dickinson et al., 2007; Schaefer et al., 2013). The present analysis confirms that cognitive deficits are present also in drug-naïve patients with schizophrenia at an early stage of the illness.

When comparing the present meta-analytic findings to previous meta-analytic findings from mostly antipsychotic medicated first episode schizophrenia patients (Mesholam-Gately et al., 2009), the effect sizes regarding the cognitive domains of verbal memory, visual memory, executive functioning (only comparing WCST) and attention (only comparing CPT) are at similar levels. The cognitive domains of working memory and speed of processing in the present meta-analysis did not include equivalent tests to Mesholam-Gately et al. (2009), however effect sizes from individual tests within these domains are still comparable. With regard to the subjects' age, education and gender proportions these two meta-analyses are similar (see Table 4 in the Supplementary data). Approximately 37% of the patients in the Mesholam-Gately et al. (2009) study were either in a medication free or drug naïve state, and twelve of the studies (corresponding to approximately 18% of the patients) included only drug-naïve patients, some of which may have been included also in the present meta-analysis. Although the samples are thus partly overlapping, the strength of the present analysis is that it confirms that some cognitive impairments are a characteristic of patients with schizophrenia, in the absence of medication.

There are to date only few and small studies examining antipsychotic treatment effects in drug-naïve patients with schizophrenia, all of them suggesting that there are no evident effects of antipsychotic treatment on cognition in these patients (Hong et al., 2002; Fagerlund et al., 2004; Hill et al., 2008; Andersen et al., 2011). However, studies directly examining the effects of antipsychotic drugs on cognition in

patients usually include medicated patients who are treated with the test drug after a short washout period. Thus, they do not employ a baseline evaluation of cognitive performance at drug free conditions (Keefe et al., 2007a,b). Although meta-analytic comparisons comparing antipsychotic medicated to unmedicated cohorts do not directly measure drug treatment effects, they may constitute an additional valuable source for information.

The broad profile of cognitive deficits may also be present in an attenuated form in unaffected first-degree relatives of patients with schizophrenia. Indeed, deficits in executive functioning have been found in healthy first-degree relatives in two meta-analyses (Szöke et al., 2005; Snitz et al., 2006). A third meta-analysis also showed, in addition to executive functioning, impairments in verbal memory and to some degree impairments in attention in the healthy first degree relatives (Sitskoorn et al., 2004). These domains can therefore be considered as candidates for a cognitive endophenotype of schizophrenia.

A limitation of the present meta-analysis is that several of the studies had not matched their samples regarding age, gender and education level. This may have influence on the results since both age and education level have been related to cognitive performance. There was thus some variability among the included samples regarding demographic characteristics as well as regarding the patients' DUP, all of which may raise questions about the heterogeneity and the representativeness of the included samples. Some domains, for example verbal memory, displayed high within domain heterogeneity indicating a large degree of variability among the cognitive tests used. Though, an important notion is that heterogeneity may also reflect actual task heterogeneity rather than between subject or between sample differences. Overall moderator analysis revealed spare results and no recurring patterns, which partly may be due to insufficient amount of observations. Publication bias was only displayed in the working memory domain, which may indicate the presence of asymmetry and bias in the literature, such as exclusion of non-significant studies. Another bias is the use of benzodiazepines that mostly were not documented in the reviewed articles, but still may have had an impact on cognition. For future research in first episode schizophrenia, it is recommended that concomitant medication is documented in more detail. Another limitation was that although different but not overlapping outcome measures from the same test were included in the analysis, these may have been correlated, since good performance is reflected in all the corresponding outcome measures of a test. Finally, patients are sometimes in stressful conditions during onset of psychosis and first admission. Such conditions may have effect on sleep, on capacity to concentrate, and also on motivation during testing.

To conclude, the results in the present meta-analysis show that antipsychotic drug-naïve patients with schizophrenia perform more poorly than healthy controls in all cognitive domains with medium to large effect sizes. Verbal memory, speed of processing and working memory were three of the domains with the greatest impairments. The results indicate the existence of significant cognitive impairments at the early stages of the illness in the absence of antipsychotic medication.

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**Contributors**

Fatouros-Bergman, H. conducted the literature searches, analysis and interpretation of data and worked with the manuscript writing; Cervenka, S. contributed to the interpretation of results and to the manuscript writing; Flyckt, L. contributed to the manuscript writing; Edman, G. advised on statistical analyses and contributed to the manuscript writing; Farde, L. contributed to the design of the study, to the interpretation of results and to the manuscript writing.

**Conflict of interest**

The authors have no conflicts of interest in relation to the subject of this study.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.schres.2014.06.034.

## References

Aleman, A., Hijman, R., de Haan, E.H., Kahn, R.S., 1999. Memory impairment in schizophrenia: a meta-analysis. Am. J. Psychiatry 156 (9), 1358–1366.

Andersen, R., Fagerlund, B., Rasmussen, H., Ebdrup, B.H., Aggernaes, B., Gade, A., Oranje, B., Glenthoj, B., 2011. Cognitive effects of six months of treatment with quetiapine in antipsychotic-naïve first-episode schizophrenia. Psychiatry Res. 187 (1–2), 49–54.

Andersen, R., Fagerlund, B., Rasmussen, H., Ebdrup, B.H., Aggernaes, B., Gade, A., Oranje, B., Glenthoj, B., 2013. The influence of impaired processing speed on cognition in first-episode antipsychotic-naive schizophrenic patients. Eur. Psychiatry.

Andreasen, N.C., Rezai, K., Alliger, R., Swayze II, V.W., Flaum, M., Kirchner, P., Cohen, G., O'Leary, D.S., 1992. Hypofrontality in neuroleptic-naive patients and in patients with chronic schizophrenia. Assessment with xenon 133 single-photon emission computed tomography and the Tower of London. Arch. Gen. Psychiatry 49 (12), 943–958.

Backman, L., Ginovart, N., Dixon, R.A., Wahlin, T.B., Wahlin, A., Halldin, C., Farde, L., 2000. Age-related cognitive deficits mediated by changes in the striatal dopamine system. The American journal of psychiatry 157 (4), 635–637.

Barak, S., 2009. Modeling cholinergic aspects of schizophrenia: focus on the antimuscarinic syndrome. Behav. Brain Res. 204 (2), 335–351.

Barch, D.M., Carter, C.S., Braver, T.S., Sabb, F.W., MacDonald III, A., Noll, D.C., Cohen, J.D., 2001. Selective deficits in prefrontal cortex function in medication-naive patients with schizophrenia. Arch. Gen. Psychiatry 58 (3), 280–288.

Bora, E., Murray, M.R., 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 (4), 744-55.

Bora, E., Lin, A., Wood, S.J., Yung, A.R., McGorry, P.D., Pantelis, C., 2014. Cognitive deficits in youth with familial and clinical high risk to psychosis: a systematic review and meta-analysis. Acta Psychiatr. Scand. 1–15.

Brickman, A.M., Buchsbaum, M.S., Bloom, R., Bokhoven, P., Paul-Odouard, R., Haznedar, M. M., Dahlman, K.L., Hazlett, E.A., Aronowitz, J., Heath, D., Shihabuddin, L., 2004. Neuropsychological functioning in first-break, never-medicated adolescents with psychosis. J. Nerv. Ment. Dis. 192 (9), 615–622.

Buchsbaum, M.S., Haier, R.J., Potkin, S.G., Nuechterlein, K., Bracha, H.S., Katz, M., Lohr, J., Wu, J., Lottenberg, S., Jerabek, P.A., et al., 1992. Frontostriatal disorder of cerebral metabolism in never-medicated schizophrenics. Arch. Gen. Psychiatry 49 (12), 935–942.

Carlsson, A., Lindqvist, M., 1963. Effect of chlorpromazine or haloperidol on formation of 3-methoxytyramine and normetanephrine in mouse brain. Acta Pharmacol. Toxicol. 20, 140–144.

Cervenka, S., Backman, L., Cselenyi, Z., Halldin, C., Farde, L., 2008. Associations between dopamine D2-receptor binding and cognitive performance indicate functional compartmentalization of the human striatum. NeuroImage 40 (3), 1287–1295.

Chan, R.C., Chen, E.Y., Law, C.W., 2006. Specific executive dysfunction in patients with first-episode medication-naive schizophrenia. Schizophr. Res. 82 (1), 51–64.

Cleghorn, J.M., Garnett, E.S., Nahmias, C., Firnau, G., Brown, G.M., Kaplan, R., Szechtman, H., Szechtman, B., 1989. Increased frontal and reduced parietal glucose metabolism in acute untreated schizophrenia. Psychiatry Res. 28 (2), 119–133.

Cropley, V.L., Fujita, M., Innis, R.B., Nathan, P.J., 2006. Molecular imaging of the dopaminergic system and its association with human cognitive function. Biol. Psychiatry 59 (10), 898–907.

DerSimonian, R., Laird, N., 1986. Meta-analysis in clinical trials. Control. Clin. Trials 7 (3), 177–188.

Dickinson, D., Ramsey, M.E., Gold, J.M., 2007. Overlooking the obvious: a meta-analytic comparison of digit symbol coding tasks and other cognitive measures in schizophrenia. Arch. Gen. Psychiatry 64 (5), 532–542.

Egger, M., Davey Smith, G., Schneider, M., Minder, C., 1997. Bias in meta-analysis detected by a simple, graphical test. BMJ 315 (7109), 629–634.

Fagerlund, B., Mackeprang, T., Gade, A., Glenthoj, B.Y., 2004. Effects of low-dose risperidone and low-dose zuclopenthixol on cognitive functions in first-episode drug-naive schizophrenic patients. CNS spectrums 9 (5), 364–374.

Farde, L., Nordstrom, A.L., Wiesel, F.A., Pauli, S., Halldin, C., Sedvall, G., 1992. Positron emission tomographic analysis of central D1 and D2 dopamine receptor occupancy in patients treated with classical neuroleptics and clozapine. Relation to extrapyramidal side effects. Arch. Gen. Psychiatry 49 (7), 538–544.

Harrison, B.J., Yucel, M., Shaw, M., Brewer, W.J., Nathan, P.J., Strother, S.C., Olver, J.S., Egan, G.F., Velakoulis, D., McGorry, P.D., Pantelis, C., 2006. Dysfunction of dorsolateral prefrontal cortex in antipsychotic-naive schizophreniform psychosis. Psychiatry Res. 148 (1), 23–31.

He, Z., Deng, W., Li, M., Chen, Z., Jiang, L., Wang, Q., Huang, C., Collier, D.A., Gong, Q., Ma, X., Zhang, N., Li, T., 2013. Aberrant intrinsic brain activity and cognitive deficit in first-episode treatment-naive patients with schizophrenia. Psychol. Med. 43 (4), 769–780.
Heinrichs, R.W., Zakzanis, K.K., 1998. Neurocognitive deficit in schizophrenia: a quantitative review of the evidence. Neuropsychology 12 (3), 426–445.
Higgins, J.P., Thompson, S.G., 2002. Quantifying heterogeneity in a meta-analysis. Stat. Med. 21 (11), 1539–1558.
Higgins, J.P., Thompson, S.G., Deeks, J.J., Altman, D.G., 2003. Measuring inconsistency in meta-analyses. BMJ 327 (7414), 557–560.
Hill, S.K., Beers, S.R., Kmiec, J.A., Keshavan, M.S., Sweeney, J.A., 2004. Impairment of verbal memory and learning in antipsychotic-naive patients with first-episode schizophrenia. Schizophr. Res. 68 (2–3), 127–136.
Hill, S.K., Reilly, J.L., Harris, M.S., Khine, T., Sweeney, J.A., 2008. Oculomotor and neuropsychological effects of antipsychotic treatment for schizophrenia. Schizophr Bull. 34 (3), 494–506.
Hong, K.S., Kim, J.G., Koh, H.J., Koo, M.S., Kim, J.H., Lee, D., Kim, E., 2002. Effects of risperidone on information processing and attention in first-episode schizophrenia. Schizophrenia research 53 (1–2), 7–16.
Hu, M., Chen, J., Li, L., Zheng, Y., Wang, J., Guo, X., Wu, R., Zhao, J., 2011. Semantic fluency and executive functions as candidate endophenotypes for the early diagnosis of schizophrenia in Han Chinese. Neurosci. Lett. 502 (3), 173–177.
Jones, H.M., Brammer, M.J., O'Toole, M., Taylor, T., Ohlsen, R.I., Brown, R.G., Purvis, R., Williams, S., Pilowsky, L.S., 2004. Cortical effects of quetiapine in first-episode schizophrenia: a preliminary functional magnetic resonance imaging study. Biol. Psychiatry 56 (12), 938–942.
Keefe, R.S., 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., C. Investigators, Neurocognitive Working G., 2007a. Neurocognitive effects of antipsychotic medications in patients with chronic schizophrenia in the CATIE Trial. Arch. Gen. Psychiatry 64 (6), 633–647.
Keefe, R.S., 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 (7), 1061–1071.
Kern, R.S., Nuechterlein, K.H., Green, M.F., Baade, L.E., Fenton, W.S., Gold, J.M., Keefe, R.S., Mesholam-Gately, R., Mintz, J., Seidman, L.J., Stover, E., Marder, S.R., 2008. The MATRICS Consensus Cognitive Battery, part 2: co-norming and standardization. Am. J. Psychiatry 165 (2), 214–220.
Lu, W., Zhang, C., Yi, Z., Li, Z., Wu, Z., Fang, Y., 2012. Association between BDNF Val66Met polymorphism and cognitive performance in antipsychotic-naive patients with schizophrenia. J. Mol. Neurosci. 47 (3), 505–510.
Mesholam-Gately, R.I., Giuliano, A.J., Goff, K.P., Faraone, S.V., Seidman, L.J., 2009. Neurocognition in first-episode schizophrenia: a meta-analytic review. Neuropsychology 23 (3), 315–336.
Nuechterlein, K.H., Green, M.F., Kern, R.S., Baade, L.E., Barch, D.M., Cohen, J.D., Essock, S., Fenton, W.S., Frese III, F.J., Gold, J.M., Goldberg, T., Heaton, R.K., Keefe, R.S., 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 (2), 203–213.
Parellada, E., Catafau, A.M., Bernardo, M., Lomena, F., Gonzalez-Monclus, E., Setoain, J., 1994. Prefrontal dysfunction in young acute neuroleptic-naive schizophrenic patients: a resting and activation SPECT study. Psychiatry Res. 55 (3), 131–139.
Ramaekers, J.G., Louwerens, J.W., Muntjewerff, N.D., Milius, H., de Bie, A., Rosenzweig, P., Patat, A., O'Hanlon, J.F., 1999. Psychomotor, cognitive, extrapyramidal, and affective functions of healthy volunteers during treatment with an atypical (amisulpride) and a classic (haloperidol) antipsychotic. J. Clin. Psychopharmacol. 19 (3), 209–221.
Saeedi, H., Remington, G., Christensen, B.K., 2006. Impact of haloperidol, a dopamine D2 antagonist, on cognition and mood. Schizophr. Res. 85 (1–3), 222–231.
Salgado-Pineda, P., Baeza, I., Perez-Gomez, M., Vendrell, P., Junque, C., Bargallo, N., Bernardo, M., 2003. Sustained attention impairment correlates to gray matter decreases in first episode neuroleptic-naive schizophrenic patients. NeuroImage 19 (2 Pt 1), 365–375.
Saykin, A.J., Gur, R.C., Gur, R.E., Mozley, P.D., Mozley, L.H., Resnick, S.M., Kester, D.B., Stafiniak, P., 1991. Neuropsychological function in schizophrenia. Selective impairment in memory and learning. Arch. Gen. Psychiatry 48 (7), 618–624.
Schaefer, J., Giangrande, E., Weinberger, D.R., Dickinson, D., 2013. The global cognitive impairment in schizophrenia: consistent over decades and around the world. Schizophr. Res. 150 (1), 42–50.
Sitskoorn, M.M., Aleman, A., Ebisch, S.J., Appels, M.C., Kahn, R.S., 2004. Cognitive deficits in relatives of patients with schizophrenia: a meta-analysis. Schizophr. Res. 71 (2–3), 285–295.
Snitz, B.E., Macdonald III, A.W., Carter, C.S., 2006. Cognitive deficits in unaffected first-degree relatives of schizophrenia patients: a meta-analytic review of putative endophenotypes. Schizophr. Bull. 32 (1), 179–194.
Szöke, A., Schürhoff, F., Mathieu, F., Meary, A., Ionescu, S., Leboyer, M., 2005. Tests of executive functions in first-degree relatives of schizophrenic patients: a meta-analysis. Psychol. Med. 35 (6), 771–782.
Takahashi, H., Kato, M., Hayashi, M., Okubo, Y., Takano, A., Ito, H., Suhara, T., 2007. Memory and frontal lobe functions; possible relations with dopamine D2 receptors in the hippocampus. NeuroImage 34 (4), 1643–1649.
van Veelen, N.M., Vink, M., Ramsey, N.F., van Buuren, M., Hoogendam, J.M., Kahn, R.S., 2011. Prefrontal lobe dysfunction predicts treatment response in medication-naive first-episode schizophrenia. Schizophrenia research 129 (2–3), 156–162.
Vernaleken, I., Kumakura, Y., Cumming, P., Buchholz, H.G., Siessmeier, T., Stoeter, P., Muller, M.J., Bartenstein, P., Grunder, G., 2006. Modulation of [$^{18}$F]fluorodopa (FDOPA) kinetics in the brain of healthy volunteers after acute haloperidol challenge. NeuroImage 30 (4), 1332–1339.
Veselinovic, T., Schorn, H., Vernaleken, I.B., Hiemke, C., Zernig, G., Gur, R., Grunder, G., 2013. Effects of antipsychotic treatment on cognition in healthy subjects. J. Psychopharmacol. 27 (4), 374–385.
Volkow, N.D., Gur, R.C., Wang, G.J., Fowler, J.S., Moberg, P.J., Ding, Y.S., Hitzemann, R., Smith, G., Logan, J., 1998. Association between decline in brain dopamine activity with age and cognitive and motor impairment in healthy individuals. Am. J. Psychiatry 155 (3), 344–349.
Wang, Q., Chan, R., Sun, J., Yao, J., Deng, W., Sun, X., Liu, X., Sham, P.C., Ma, X., Meng, H., Murray, R.M., Collier, D.A., Li, T., 2007. Reaction time of the Continuous Performance Test is an endophenotypic marker for schizophrenia: a study of first-episode neuroleptic-naive schizophrenia, their non-psychotic first-degree relatives and healthy population controls. Schizophr. Res. 89 (1–3), 293–298.
Zhang, X.Y., Chen da, C., Xiu, M.H., Yang, F.D., Haile, C.N., Kosten, T.A., Kosten, T.R., 2012. Gender differences in never-medicated first-episode schizophrenia and medicated chronic schizophrenia patients. J. Clin. Psychiatry 73 (7), 1025–1033.