

# Early cognitive basic symptoms are accompanied by neurocognitive impairment in patients with an 'at-risk mental state' for psychosis

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## Abstract

**Aim:** Patients with an increased risk for psychosis ('at-risk mental state' (ARMS)) present various neurocognitive deficits. Not least because of differences in identifying the ARMS, results of previous studies are inconsistent. In most studies ARMS-patients are classified by the experience of attenuated psychotic symptoms (APS) and/or brief limited intermittent psychotic symptoms (BLIPS). Few studies additionally assessed cognitive basic symptoms (BS). A comprehensive assessment in the very early stage of the ARMS is missing.

**Methods:** In the present study we characterized ARMS-patients for cognitive BS (ARMS-BS), APS and BLIPS (ARMS-A/B) according to the Early Recognition Inventory based on IRAOS (ERIRAOS). Furthermore, we assessed neurocognitive deficits using the MATRICS consensus cognitive battery for schizophrenia with a primary hypothesis regarding working memory performance. Groups of 38 ARMS-

patients and 38 healthy controls were matched for age, gender, education and premorbid verbal intelligence.

**Results:** Between-group comparisons revealed significant poorer working memory performance in addition to lower verbal learning and problem solving, slower processing speed and lower global neurocognitive functioning in ARMS-patients as compared to controls. ARMS-BS did not differ from ARMS-A/B.

**Conclusions:** These results underscore the presence of cognitive limitations in patients only presenting with cognitive BS. Knowledge of these early cognitive deviations supports the inclusion of early ARMS-stages into a comprehensive concept of the psychosis risk state. Therapeutic interventions already applied at this stage might prevent deterioration of constraints. Longitudinal and interventional studies investigating the interaction of cognitive BS and neurocognitive as well as metacognitive deficits are warranted.

**Key words:** at-risk mental state, cognition, ERIRAOS, prodrome, working memory.

## INTRODUCTION

Schizophrenia patients typically display psychotic positive, as well as negative symptoms and a broad range of neurocognitive deficits.<sup>1</sup> These determine the prognosis of social and vocational rehabilitation to a large extent.<sup>2,3</sup> Neurocognitive deficits mainly concern the domains attention and vigilance, executive functioning and problem solving, working memory, processing speed as well as verbal and visual learning.<sup>4</sup> Among these domains, working memory impairment has been found to be a central feature of schizophrenia.<sup>5</sup> This impairment is even discussed as an endophenotypic marker of the illness<sup>6</sup> as it has been consistently found in patients with schizophrenia<sup>7</sup> and unaffected relatives.<sup>8</sup> Furthermore, it seems to be state independent<sup>9</sup> and specific to schizophrenia spectrum disorders.<sup>6</sup>

Several prior studies have reported findings about neurocognitive deficits in the 'at-risk mental state' (ARMS) for psychosis, e.g. in working memory, verbal memory, executive control and processing speed.<sup>10-18</sup> These results are summarized in a recent meta-analysis<sup>19</sup> which states that neurocognitive deficits are evident before the first onset of psychosis and do not decline over a 5-year period of illness. Compatible with findings in patients with schizophrenia, working memory impairment has been discussed to be one core neurocognitive deficit in the ARMS, differentiating between those patients with and without a transition to psychosis.<sup>20</sup> Visuospatial<sup>21-23</sup> as well as verbal working memory abilities<sup>13,24,25</sup> seem to be affected. Furthermore, processing speed deficits form an important dimension within the pathogenesis of psychosis. Poor performance in an ultra-high risk community sample,<sup>26</sup> in a birth cohort study<sup>27</sup> and in adolescents who later developed a schizophreniform disorder<sup>28</sup> propose a potential predicting function of psychotic experiences. Supporting these findings, a longitudinal study showed that the neurocognitive performance of ARMS-patients who later experienced a transition to psychosis only deteriorated in the domains working memory and processing speed over a 6-months course.<sup>14</sup>

Most studies classify ARMS-patients by 'ultra-high risk' (UHR)-criteria for schizophrenia spectrum disorders, diagnosed by the presence of attenuated psychotic symptoms (APS) and/or brief limited intermittent psychotic symptoms (BLIPS) or by a genetic risk and a deterioration syndrome.<sup>29,30</sup> These symptoms are generally assessed by the 'Structured Interview for Prodromal Syndromes' (SIPS)<sup>31</sup> including the 'Criteria Of Prodromal Syndromes' (COPS) or the

'Comprehensive Assessment of At Risk Mental States' (CAARMS).<sup>32</sup> Hence, the majority of reviews and meta-analyses on neurocognitive deficits in the ARMS mainly include studies defining the ARMS according to SIPS/SOPS or CAARMS.<sup>11,19,33,34</sup>

However, Huber, Gross and Klosterkötter described cognitive basic symptoms (BS)<sup>35</sup> that already occur in early ARMS-stages.<sup>36,37</sup> They thereby added an important symptom cluster which the UHR-definition does not account for. Cognitive BS display the core symptoms of the 'Bonn Scale for the Assessment of Basic Symptoms' (BSABS)<sup>35</sup> and the 'Schizophrenia Proneness Instrument – Adult version' (SPI-A)<sup>38</sup> and are also represented in the ERiraos (Early Recognition Inventory for the Retrospective Assessment of the Onset of Schizophrenia based on IRAOS)<sup>39-41</sup> ERiraos aims at the feasible detection of an increased risk for psychosis by concentrating on the presence of symptoms during the last 12 months, and provides a detailed assessment of APS, BLIPS and cognitive BS within one scale. In comparison to the CAARMS, ERiraos has been demonstrated to be equally sensitive in the detection of APS and BLIPS. With the inclusion of cognitive BS it further allows for a high sensitivity in the assessment of the whole spectrum of ARMS-symptoms and thereby reduces false-negative attributions.<sup>41</sup> In summary, as cognitive BS have become increasingly important in prodromal research,<sup>18,37,42</sup> it seems crucial to integrate them into the identification of ARMS-patients when assessing neurocognitive deficits. So far, relatively few studies assessed cognitive BS when analyzing neurocognitive performance in the ARMS and reported inconsistent results.<sup>10,13,43,44</sup> Furthermore different scales were used in these studies in order to assess the whole spectrum of symptomatology.

The aim of the present study was to assess neurocognitive deficits in an ARMS-sample that was characterized by the final version of the ERiraos, focusing on cognitive BS in addition to APS and BLIPS (see methods for details). Our core hypothesis was that ARMS-patients characterized by ERiraos display a deficit in the domain working memory as well as in the two subtests of verbal and spatial working memory. Furthermore, we assumed to find a deficit regarding global ('composite') neurocognitive functioning. Secondary endpoints included between-group comparisons of further cognitive domains, between-group comparisons of ARMS-subsamples (patients with cognitive BS only

(ARMS-BS) vs. patients with APS and/or BLIPS (ARMS-A/B)), and finally a description of the interplay of cognitive BS and neurocognitive deficits.

## METHODS

### Participants

The present study was approved by the local ethics committee of the Medical Faculty Mannheim of the University of Heidelberg (AZ 2009-296N-MA). Patients met the pre-defined inclusion criteria: (i) attribution to ARMS according to ERiraos<sup>39-41</sup> (sum score  $\geq 30$  and/or presence of at least two cognitive BS and/or at least one APS and/or at least one BLIPS); (ii) age between 18 and 40 years; (iii) ability to provide written informed consent; and (iv) sufficient German language skills. Patients who fulfilled the criteria for a first episode of psychosis, for substance dependence excluding nicotine, or for other disorders of the central nervous system requiring treatment were excluded. A number of 38 ARMS-patients were included into the study. None of them were treated with antipsychotics. Stable pre-medication with antidepressants (citalopram ( $n=2$ ), mirtazapine ( $n=2$ ), sertraline ( $n=2$ ), paroxetine ( $n=1$ ), duloxetine ( $n=1$ ), trimipramine ( $n=2$ )) was allowed. Because of anxiety or agitation four patients were treated with low doses of lorazepam. Three patients had a positive family history of schizophrenia in first degree relatives and further six patients in second degree relatives. A number of 16 patients reported cannabis abuse in the past. Six of them indicated intermittent or one-time abuse of further substances (hallucinogens=2, amphetamine=5, cocaine=3). In any case, last drug use was at least four weeks prior to study entry. None of them fulfilled the criteria for drug addiction. A number of 38 healthy control subjects (HC) were matched for gender, age, levels of education and premorbid verbal intelligence (Table 1), had no positive family history of schizophrenia, bipolar disorder or suicide in first-degree relatives, and did neither have any previous or current psychiatric disorders according to the M.I.N.I. (Mini-International Neuropsychiatric Interview) nor any former or present psychopharmacological treatment.

### Psychometric rating scales

ARMS-symptoms and general psychopathology were characterized by trained and certified clinicians using ERiraos, PANSS (Positive and

Negative Syndrome Scale) and PSYRATS (Psychotic Symptoms Rating Scale). PANSS composite scores<sup>45</sup> as well as the PANSS five factor-model<sup>46</sup> were evaluated. We further assessed negative symptoms (Scale for the Assessment of Negative Symptoms: SANS), comorbid depressive symptoms (Calgary Depression Scale for Schizophrenia: CDSS), general severity of illness (Clinical Global Impression: CGI) and psychosocial functioning (Global Assessment of Functioning: GAF; Personal and Social Performance Scale: PSP).

### Neurocognitive characterization

Cognitive abilities were assessed using the MATRICS consensus cognitive battery (MCCB) for schizophrenia,<sup>47</sup> that includes 10 tests representing seven domains, namely working memory (Letter-Number Sequencing, Spatial Span), verbal (Hopkins Verbal Learning Task revised) and visual learning (Brief Visuo-Spatial Memory Test revised), speed of processing (Trail Making Test version A, Symbol Coding, Verbal Fluency), problem solving (Mazes), social cognition (Meyer-Salovey-Caruso Emotional Intelligence Test), and vigilance (Continuous Performance Test – identical pairs). Additionally, attention and executive functioning were assessed using the Trail Making Test, version B (TMT-B) and the Wisconsin Card Sorting Test (WCST). Estimated premorbid verbal intelligence was assessed using the Multiple Choice Word Test, version B (MWT-B).

### Statistical evaluation

Based on existing data,<sup>48</sup> we estimated the required sample size to detect group differences using the statistical software G\*power 3.1.<sup>49</sup> Given a significance level of 0.05 and an effect size of  $d=0.74$ , at least 24 participants per group were considered sufficient for achieving a power of 0.8. Statistical analyses were conducted using the Statistical Package for Social Sciences (IBM SPSS version 20.0, Chicago, IL, US). Neurocognitive performance was expressed in terms of standardized  $t$ -values. Single tests representing the same domain contributed equally to domain scores. Furthermore, a global composite score was calculated, also indicated by a  $t$ -value.<sup>50</sup> Descriptive statistics included means and standard deviations. We tested for non-normal distributions of parameters using histograms and the Kolmogorov-Smirnov test. Scores of two domains were slightly skewed to the right, namely *problem solving* within the control group and

TABLE 1. Socio-demographic and psychopathological characteristics of study samples

	Patients (n = 38)	Controls (n = 38)	Comparison
<b>Socio-demographics</b>			
Age	22.9 ± 4.17	24.3 ± 5.78	$t(74) = -1.206, p = 0.232$
Gender (female/male)	13/25	12/26	Fisher exact: $X^2(1) = .06, p = 1.000$
School years	11.2 ± 1.56	11.6 ± 1.48	$t(74) = -1.208, p = 0.231$
<b>MWT-B</b>			
Raw score	23.9 ± 4.70	24.0 ± 5.72	$t(74) = -0.110, p = 0.913$
Estimated verbal IQ	96.2 ± 10.67	97.5 ± 13.27	$t(74) = -0.448, p = 0.656$
<b>ERlraos</b>			
Sum score	42.8 ± 15.61	n.a.	n.a.
Early ARMS/late ARMS	11/27	n.a.	n.a.
<b>PANSS</b>			
Total score	61.3 ± 11.88	n.a.	n.a.
Positive symptoms	12.8 ± 4.06	n.a.	n.a.
Negative symptoms	13.5 ± 5.17	n.a.	n.a.
Global psychopathology	35.1 ± 6.83	n.a.	n.a.
<b>Additional psychometric scales</b>			
SANS	31.2 ± 21.38	n.a.	n.a.
CDSS	6.7 ± 4.32	n.a.	n.a.
PSP	57.5 ± 15.76	n.a.	n.a.
GAF	48.5 ± 10.77	n.a.	n.a.
CGI-Severity	4.1 ± 0.56	n.a.	n.a.
<b>PSYRATS</b>			
Conviction	1.3 ± 1.51	n.a.	n.a.
Sum score	8.18 ± 7.9	n.a.	n.a.

Data is reported as mean ± standard deviation (SD) or frequencies. Abbreviations: ARMS, At-Risk Mental State; CDSS, Calgary Depression Scale for Schizophrenia; CGI, Clinical Global Impression; ERlraos, Early Recognition Inventory based on IRAOS; GAF, Global Assessment of Functioning; IQ, intelligence quotient; IRAOS, Interview for the Retrospective Assessment of the Onset of Schizophrenia and Other Psychoses; MWT-B, Multiple Choice Word Test (version B); n.a., not applicable; PANSS, Positive and Negative Syndrome Scale; PSP, Personal and Social Performance Scale; PSYRATS, Psychotic Symptoms Rating Scale; SANS, Scale for the Assessment of Negative Symptoms.

*visual learning* within both groups. Between-group comparisons were performed with Student's *t*-test or univariate analyses of variance. Because group sizes were equal we assumed a robustness of these tests against non-normality.<sup>51,52</sup> In a second group-comparison, all *t*-values were transformed into dichotomous variables to either represent deficient (*t*-value < 40) or normal-range (*t*-value ≥ 40) scores. These were compared using Fisher's Exact tests.

Correlations were analysed with Pearson's correlation coefficient (*r*) or Spearman rank correlations. Linear regression analyses were performed using the 'Enter' method to analyse the interplay between ARMS symptoms and neuropsychological performance. Because of the number of comparisons, Bonferroni-correction for multiple testing was applied for the exploratory data analysis, which included all further MCCB domains.

## RESULTS

### Participants

Socio-demographic and psychometric data are provided in Table 1. There were no significant differences regarding age, gender, education and premorbid verbal intelligence. Patients were characterized as moderately affected according to PANSS, PSYRATS and ERIRaos. The mean ERIRaos sum score was  $42.8 \pm 15.61$ . Eleven patients were attributed to ARMS-BS and 27 patients to ARMS-A/B.

### Between group comparisons

Regarding working memory, ARMS-patients ( $49.34 \pm 9.10$ ) displayed a significant deficit compared to HCs ( $55.18 \pm 10.04$ ;  $T = -2.66$ ,  $df = 74$ ,  $P = 0.010$ , 95% CI  $[-10.22, -1.46]$ ,  $d = 0.610$ ). Regarding the differentiation between spatial

and verbal working memory, ARMS-patients performed significantly worse in the spatial span-task ( $50.39 \pm 10.04$  vs.  $57.16 \pm 9.80$ ,  $T = 2.97$ ,  $df = 74$ ,  $P = 0.004$ , 95% CI  $[2.23, 11.30]$ ,  $d = 0.682$ ), but no significant difference emerged for the letter-number-sequencing ( $48.32 \pm 8.16$  vs.  $51.26 \pm 10.17$ ,  $T = 1.39$ ,  $df = 74$ ,  $P = 0.168$ , 95% CI  $[-1.27, 7.16]$ ,  $d = 0.320$ ). Furthermore, a between group comparison of global ('composite') neurocognitive functioning revealed a significant lower performance in ARMS-patients (ARMS:  $43.3 \pm 8.69$  vs. HCs:  $51.1 \pm 9.37$ ;  $T = -3.76$ ,  $df = 74$ ,  $p < 0.001$ , 95% CI  $[-11.92, -3.66]$ ,  $d = 0.86$ ) (Table 2).

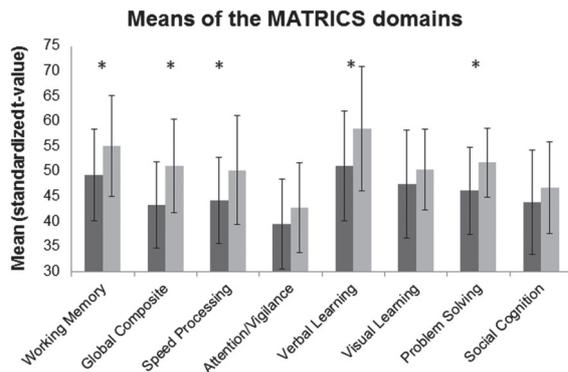
ARMS-patients and HCs were further compared regarding additional MATRICS domains (Fig. 1) as well as TMT-B and WCST. After correction for multiple testing we observed significant group differences regarding processing speed, verbal learning and problem solving (Table 2). A comparison

TABLE 2. Neurocognitive characteristics of study samples

	Patients ( $n = 38$ )	Controls ( $n = 38$ )	Comparison
<b>MATRICES test battery</b>			
Working Memory (LNS, Spatial Span)	$49.34 \pm 9.10$	$55.18 \pm 10.04$	$T(74) = -2.66$ , $p = 0.010$
Processing Speed (TMT-A, BACS-SC, Fluency)	$44.24 \pm 8.68$	$50.24 \pm 10.87$	$F(1, 74) = 7.072$ , $p = 0.010$
Verbal Learning(HVLT-R)	$51.13 \pm 10.98$	$58.53 \pm 12.40$	$F(1, 74) = 7.572$ , $p = 0.007$
Visual Learning (BVMT-R)	$47.42 \pm 10.79$	$50.42 \pm 8.05$	$F(1, 74) = 1.837$ , $p = .174$
Planning and Problem Solving (NAB-Mazes)	$46.16 \pm 8.70$	$51.76 \pm 6.85$	$F(1, 74) = 9.743$ , $p = 0.003$
Vigilance (CPT-IP)	$39.53 \pm 9.02$	$42.82 \pm 9.02$	$F(1, 74) = 2.528$ , $p = .116$
Social Cognition (MSCEIT)	$43.84 \pm 10.45$	$46.71 \pm 9.15$	$F(1, 74) = 1.622$ , $p = .207$
Global Composite	$43.34 \pm 8.69$	$51.13 \pm 9.37$	$T(74) = -3.759$ , $p < 0.001$
<b>TMT-B (sec)</b>	$59.42 \pm 17.34$	$56.84 \pm 17.82$	$F(1, 74) = 0.409$ , $p = 0.525$
<b>WCST</b>			
Total Errors (%)	$20.15 \pm 7.33$	$18.33 \pm 5.73$	$F(1, 74) = 1.457$ , $p = 0.231$
Perseveration Score (%)	$17.75 \pm 13.95$	$16.55 \pm 15.42$	$F(1, 74) = 0.127$ , $p = 0.723$
Concept perseverations	$0.76 \pm 1.15$	$0.53 \pm 0.89$	$F(1, 74) = 1.007$ , $p = 0.319$
Failure to maintain set	$0.79 \pm 1.28$	$0.76 \pm 1.32$	$F(1, 74) = 0.008$ , $p = 0.930$

Data is reported as mean  $\pm$  standard deviation (SD). Domain scores of the MATRICS domains are reported as standardized  $t$ -values. Bonferroni correction for multiple testing was applied for all MATRICS domains except 'Working Memory' and 'Global Composite', because these were tested as separate core hypotheses. Abbreviations: BACS-SC, Brief Assessment of Cognition in Schizophrenia, Symbol Coding; BVMT-R, Brief Visual Memory Test Revised; CPT-IP, Continuous Performance Test, Identical Pairs; HVLT-R, Hopkins Verbal Learning Task Revised; LNS, Letter-Number-Sequencing; MATRICS, Measurement and Treatment Research to Improve Cognition in Schizophrenia; MSCEIT, Meyer-Salovey-Caruso Emotional Intelligence Test; NAB, Neuropsychological Assessment Battery; n.s., not significant; sec, seconds; TMT-A or -B, Trail Making Test (version A and B); WCST, Wisconsin Card Sorting Test.

FIGURE 1. Means of standardized *t*-values of the MATRICS domains. Bonferroni correction for multiple testing was applied for all MATRICS domains except 'Working Memory' and 'Global Composite', because these were tested as separate hypotheses. Abbreviations: ARMS, At-Risk Mental State; AttVig, Attention and vigilance; Comp, global ('composite') neurocognitive functioning; MATRICS, Measurement and Treatment Research to Improve Cognition in Schizophrenia; PrblmS, Problem Solving; SclCgn, Social Cognition; SpdPr, Processing speed; VisL, Visual Learning; VrbLL, Verbal Learning; WM, Working memory; \* significant, ■ ARMS and □ Controls.



of the frequencies of deficits revealed no significant results. There was a trend visible for problem solving ( $X(1, n=76) = 4.145, P = .086$ ).

Within the secondary endpoints, we stratified the ARMS-group into the subgroups ARMS-A/B (with ( $n=20$ ) or without ( $n=7$ ) coexisting BS) or ARMS-BS ( $n=11$ , without any APS or BLIPS). Univariate analyses of variance revealed significant group-differences for working memory (HC:  $55.18 \pm 10.04$ , BS:  $48.91 \pm 10.26$ , APS/BLIPS:  $49.52 \pm 8.79$ ;  $F(2,73) = 3.5, P = 0.035, \eta_p^2 = .087$ ) and for global ('composite') neurocognitive functioning (HC:  $51.13 \pm 9.37$ , BS:  $42.27 \pm 10.60$ , APS/BLIPS:  $43.78 \pm 7.96$ ;  $F(2,73) = 7.096, P = 0.002, \eta_p^2 = .163$ ). Post-hoc comparisons (least square differences) revealed a trend towards significance between controls and ARMS-BS ( $P = .061, 95\% \text{ CI } [-0.31, 12.86]$ ) in working memory performance, but no difference between ARMS-BS and ARMS-A/B ( $P = .860, 95\% \text{ CI } [-7.98, 4.97]$ ). Regarding the global neurocognitive functioning, HCs significantly differed from ARMS-BS ( $P = .006, 95\% \text{ CI } [2.66, 15.06]$ ), but again no differences between ARMS-BS and ARMS-A/B became apparent ( $P = .645, 95\% \text{ CI } [-7.98, 4.97]$ ). Because the ARMS-BS group was rather small, we added chi-squared tests and compared the three experimental groups according to their working memory and global neurocognition performance, both categorized by a median split. The results were significant for working memory (working memory:  $X^2(2, n=76) = 7.877,$

$P = .019, \text{Cramer's } V = .322$ ; composite score:  $X^2(2, n=76) = 4.455, P = .108, \text{Cramer's } V = .242$ ). Further analyses revealed a significant difference between HC and ARMS-BS ( $X^2(2, n=49) = 5.168, P = .023, \text{Cramer's } V = .325$ ) but not between ARMS-BS and ARMS-A/B ( $X^2(2, n=38) = 0.331, P = .565, \text{Cramer's } V = .093$ ) for working memory. ARMS-BS patients were more frequently found in the cell with lower working memory performance compared to controls.

Three regression models were run to identify if symptomatology predicts working memory. All were non-significant. The first one included the number of cognitive BS ( $F(1, 36) = .004, P = .948$ ), the second one included a separation of cognitive BS into cognitive disturbances and perceptual disturbances ( $F(2, 35) = .037, P = .964$ ) and the third model included the number of cognitive BS, APS and BLIPS ( $F(3, 34) = .226, P = .878$ ).

Because depressive symptoms are known to interfere with neurocognitive performance, we evaluated possible confounding effects following criteria suggested by Addington and colleagues.<sup>53</sup> Comparing the ARMS-subgroups with (ARMS+D:  $\text{CDSS} > 6; n = 18$ ) versus without (ARMS-D:  $\text{CDSS} \leq 6; n = 20$ ) clinically relevant depressive symptoms, a group difference in working memory performance became apparent (ARMS+D:  $52.67 \pm 8.51$  vs. ARMS-D:  $46.35 \pm 8.76$ ;  $T = -2.25, df = 36, P = .031, 95\% \text{ CI } [-12.01, -0.62], d = .516$ ). Regarding the global composite score no significant differences occurred (ARMS+D:  $45.39 \pm 9.36$  vs. ARMS-D:  $41.5 \pm 8.76$ ;  $T = -1.40, df = 36, P = 0.171, 95\% \text{ CI } [-9.54, 1.76], d = .321$ ).

Furthermore, we evaluated potential effects of lorazepam or former cannabis abuse. A comparison of cognitive task performance in the ARMS-subgroups with versus without anxiolytic medication ( $P = .58, 95\% \text{ CI } [-12.54, 7.16]$ ) as well as with versus without cannabis abuse ( $P = .18, 95\% \text{ CI } [-1.95, 10.04]$ ) revealed no significant group differences.

## Correlation analyses

Regarding the ARMS-group we evaluated relations of neurocognition with depressive symptoms. We found working memory significantly correlated with CDSS ( $r = 0.352, P = 0.030$ ) as well as the PANSS single item G6 (Depression) ( $\rho = 0.409, P = 0.011$ ). Regarding the PANSS composite subscore 'Depression' a trend towards significance was shown ( $r = 0.315, P = 0.054$ ). There were no significant correlations between working memory or global ('composite') neurocognitive functioning and other psychopathological measures (e.g. ERIs total

score, PANSS composite scores, scores of PANSS five-factor model, GAF).

## DISCUSSION

Patients with schizophrenia display neurocognitive deficits.<sup>1,4-6</sup> Working memory impairment has been discussed as a potential endophenotypic marker of schizophrenia spectrum disorders<sup>6</sup> and is therefore expected to be already present in ARMS-patients. In line with our hypothesis, a lower working memory performance was found in the ARMS-group compared to HCs. This result is consistent with a meta-analysis by Fusar-Poli and colleagues.<sup>34</sup> Furthermore, our results indicated a significant group difference for the visuospatial but not for the verbal component of working memory. This accords findings of Wood and colleagues<sup>23</sup> who found distinct spatial working memory deficits in UHR-patients which were even more pronounced in patients who later converted to psychosis. Similarly, a meta-analysis by Lee and Park discusses robust findings of impairment in the visuospatial domain in patients with schizophrenia.<sup>5</sup> This result gives implications for the development of an optimized assessment of cognitive deficits in the early stages of psychosis, with a focus on visuospatial working memory functioning. There are other studies in contrast, summarized in a recent review,<sup>54</sup> which could not find working memory deficits in similar samples of ARMS-patients with cognitive BS, APS and/or BLIPS,<sup>10,44,55,56</sup> although the latter one nevertheless found the performance between groups to reach medium effect sizes. Results regarding visual working memory in ARMS-patients are likewise inconsistent.<sup>55,56</sup> Importantly, though working memory performance in ARMS-patients was lower than that of controls in this present study, we did not reveal deficient scores in terms of normative *t*-values. These contradictions might be explained in the light of work by Pukrop et al.<sup>57</sup> who found that working memory is actually a measure of three distinct functions: a general comparator function, an attentional resource allocation function, and a maximum capacity storage function. The implementation of a variety of working memory tasks which might be based on different of these underlying functions could therefore lead to diverging results.

Besides working memory impairments, our findings indicated a lower global ('composite') neurocognitive functioning and deficits in the domains of processing speed, verbal learning and problem solving in the ARMS. These results are in line with independent observations<sup>14,19,20,55,56</sup> and a comprehensive review<sup>58</sup>

of ARMS-patients and in turn support the sensitive characterization of the ARMS using ERIs. Again, performance of ARMS-patients in these three neuropsychological domains was not deficient in terms of *t*-values, compared to the normative sample.<sup>59</sup> The frequency analyses demonstrated an identical pattern. Only the problem solving performance tended to be more deficient in the ARMS-group. It was suggested that the measures of processing speed, verbal learning and verbal fluency might help to improve predictions of transitions to psychosis<sup>54,55</sup> and more pronounced impairment was found in patients with a first episode of psychosis.<sup>48,56</sup> Therefore, we reason that decreased cognitive performance in these domains is a clinically relevant feature of ARMS-patients even if scores do not indicate a clear deficit. In an attempt to explain diverging results between studies, a very important consideration is the use of varying diagnostic tools. This was the first study to examine neurocognition based on the current version of ERIs.<sup>41</sup> Furthermore, as the MCCB is a cognitive battery which was build up for patients with schizophrenia<sup>59</sup> the tests might not all be sensitive enough to detect deficits in the ARMS in all domains. The same has been suggested for the WCST.<sup>60</sup> Differing compositions of ARMS-patients as well as the general heterogeneity within ARMS-groups between studies potentially lead to findings of more or less severe neurocognitive deficits. It seems necessary to report the proportion of patients within the separate ARMS-groups when analysing merged groups.

Up to date, inconsistent results exist about the association between neurocognitive impairment and the conversion to psychosis.<sup>10,16,17,23,34</sup> Some studies suggested that the largest impairment occurs before psychosis onset.<sup>10,19</sup> In our cross-sectional analysis, no associations between symptomatology and working memory or global neurocognitive performance were discovered and symptomatology did not predict neurocognitive impairment. However, we examined the heterogeneous ARMS-group more closely and revealed differences in working memory and global cognitive performance between the control group and both ARMS subgroups. No differences were found between ARMS-BS and ARMS-A/B. Somewhat dissenting results were found regarding global neurocognition when the second analysis strategy was implemented. ARMS-subgroups did not differ from controls anymore. A potential reason can be found in the loss of statistical power by a categorization of the variable. More even because the variable already just represented a summarized value of different cognitive functions.

The present findings underscore that early ARMS-stages, characterized by the experience of cognitive basic symptoms, are already accompanied by similar neurocognitive impairment as patients in later stages. Findings of Koutsouleris and colleagues support this implication. The authors could differentiate ARMS-BS from healthy controls on the basis of visual working memory and verbal learning using a machine-learning procedure.<sup>61</sup> ARMS-A/B were differentiated from healthy controls mainly by means of verbal IQ, executive functions and processing speed. Thus, very similar neurocognitive domains were identified in their study and ours. In another study, impairment was slightly more severe in patients in late ARMS-compared to early ARMS-stages but without statistical significance.<sup>38</sup> Taken together, we reason that the assessment of the whole spectrum of ARMS-symptoms, when defining ARMS-samples, is highly important in multiple ways: As Ruhrmann and colleagues showed, considering both UHR-criteria and cognitive disturbances (COGDIS) improves the sensitivity for predicting psychotic transitions.<sup>42</sup> Likewise, another comparison of the exclusive assessment of UHR-criteria with a combination of UHR-criteria and COGDIS revealed improved sensitivity for the use of both criteria.<sup>62</sup> As the present results emphasize, the composition of cognitive BS and UHR-criteria is also reasonable to sensitively assess cognitive impairment, even before a transition to psychosis. This is in line with a recent study showing that cognitive BS and APS in combination with a processing speed deficit turned out to be an 'optimized stratified risk assessment'.<sup>18</sup> The detection of working memory constraints in the ARMS indicates the need for effective early therapeutic interventions, such as cognitive remediation-trainings, to improve functional outcome.<sup>2</sup>

The comparison of the subgroups ARMS+D and ARMS – D revealed lower working memory scores in the ARMS – D group. Furthermore, our findings revealed significant positive correlations between working memory and clinical relevant depression (CDSS, PANSS), suggesting that subjects with higher depression scores might have better working memory performance. These findings were surprising, as prior research has discussed depression to go along with impaired working memory function.<sup>63–65</sup> Other studies did not find any association.<sup>13,66</sup> So far, heterogeneity within the merged ARMS-sample cannot be excluded and it is open to ask, whether depressive symptoms might be linked to an altered transition risk to psychosis. Also, the possibility that the ARMS+D group mainly

consisted of patients who will develop an affective disorder should be regarded. With this in mind, the present results might support prior findings which showed that depressed patients had better global neurocognitive<sup>67</sup> and working memory skills<sup>68</sup> than patients with schizophrenia or ARMS-patients who later converted to psychosis.<sup>69</sup>

## LIMITATIONS

This study is limited because of the cross-sectional design, the mono-centric approach, the lack of psychiatric control groups and the lack of data regarding transitions to psychosis. The small sample size of the individual ARMS-subgroups might have increased beta-error and therefore might have covered possibly existing working memory differences between controls and ARMS-BS. Longitudinal studies are necessary to associate cognitive deficits with the risk for transition and to investigate the longitudinal changes of these deficits.

## CONCLUSION

The early and likewise valid identification and the comprehensive characterization of ARMS-patients currently display some of the crucial topics in schizophrenia research.<sup>37</sup> The present study is the first to focus on working memory abilities in ARMS-patients characterized by ERIs. Working memory abilities were significantly lower in ARMS-patients compared to controls, lower in ARMS-BS compared to controls and no differences became evident between ARMS-BS and ARMS-A/B. This provides new support for the hypothesis that working memory deficits might be cognitive markers of psychosis development.<sup>6,70</sup> The results further suggest that not working memory alone but rather a combination of cognitive malfunctions, most importantly problem solving, processing speed and verbal learning, contribute to cognitive impairment in the ARMS. Forthcoming studies on neurocognition in the ARMS should reflect the entire spectrum of symptoms including cognitive BS concepts. Longitudinal studies should investigate if a combination of cognitive BS assessed with ERIs and the identified cognitive domains might allow for an early estimation of the transition risk and might include other psychiatric control groups to explore the specificity of these deficits to psychosis. Not least because of the cognitive impairment, therapeutic interventions should already be implemented in the early ARMS

to improve the symptomatology and circumvent possible deteriorations of existing constraints.

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