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Reduced activation in the ventral striatum during probabilistic decision-making in patients in an at-risk mental state

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Background: Patients with schizophrenia display metacognitive impairments, such as hasty decision-making during probabilistic reasoning — the "jumping to conclusion" bias (JTC). Our recent fMRI study revealed reduced activations in the right ventral striatum (VS) and the ventral tegmental area (VTA) to be associated with decision-making in patients with schizophrenia. It is unclear whether these functional alterations occur in the at-risk mental state (ARMS). **Methods:** We administered the classical beads task and fMRI among ARMS patients and healthy controls matched for age, sex, education and premorbid verbal intelligence. None of the ARMS patients was treated with antipsychotics. Both tasks request probabilistic decisions after a variable amount of stimuli. We evaluated activation during decision-making under certainty versus uncertainty and the process of final decision-making. **Results:** We included 24 AMRS patients and 24 controls in our study. Compared with controls, ARMS patients tended to draw fewer beads and showed significantly more JTC bias in the classical beads task, mirroring findings in patients with schizophrenia. During fMRI, ARMS patients did not demonstrate JTC bias on the behavioural level, but showed a significant hypoactivation in the right VS during the decision stage. **Limitations:** Owing to the cross-sectional design of the study, results are constrained to a better insight into the neurobiology of risk constellations, but not pre-psychotic stages. Nine of the ARMS patients were treated with antidepressants and/or lorazepam. **Conclusion:** As in patients with schizophrenia, a striatal hypoactivation was found in ARMS patients. Confounding effects of antipsychotic medication can be excluded. Our findings indicate that error prediction signalling and reward anticipation may be linked to striatal dysfunction during prodromal stages and should be examined for their utility in predicting transition risk.

Introduction

Patients with schizophrenia have metacognitive deficits — reduced competence to control their cognition ("thinking about one's thinking"). They have impaired ability to appraise and weigh information effectively; to select appropriate responses, including decisions based on perceptions; to cope with cognitive limitations; and to build up mental states.[1,2] One aspect of these metacognitive deficits is a tendency toward hasty decision-making during probabilistic reasoning — the "jumping to conclusion" bias (JTC), which is generally assessed using the beads task. This task requests a probabilistic decision after a variable amount of stimuli, and JTC is usually defined as requiring only 1–2 stimuli to make a decision.[3–5] The theory of "disturbed error-dependent updating of inferences and beliefs about the world" in patients with schizophrenia[6] and findings on the JTC bias suggest that metacognitive impairments play a relevant role in the development of delusions.[7–11] Furthermore, limited data gathering and the tendency to disregard evidence were recently found to be maintaining factors for delusions.[12]

In general, pathogenic studies in patients with schizophrenia are often limited owing to several illness- and treatment-related confounds. To study underlying cognitive processes of psychotic disorders, it seems crucial to assess medication-naive patients with first-episode psychosis (FEP).[13] It is even more interesting to investigate patients in the at-risk mental state (ARMS), because findings provide insight into the development of pathology over time. These patients are characterized by the occurrence of cognitive basic

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symptoms, attenuated psychotic symptoms (APS) and/or brief limited intermittent psychotic symptoms (BLIPS).[14] On average, about 22% of the patients meeting ARMS criteria experience a transition to psychosis later on.[15–17]

Preliminary results allow first insight into the importance of metacognitive deficits in ARMS based, for instance, on the metacognitive questionnaire.[18,19] Barkus and colleagues[20] showed metacognitive deficits in ARMS patients and individuals with pronounced schizotypic traits. Because JTC deficits were also found in healthy first-degree relatives, remitted patients and individuals with pronounced schizotypic characteristics,[21] they were suggested to be trait markers for schizophrenia. Several studies analyzed the JTC bias and its association with neurocognitive abilities in ARMS patients.[22–25] Most of these studies characterized ARMS patients according to APS and BLIPS.[23] However, including cognitive basic symptoms[26] in the characterization of patients seems to be a necessary and complementary approach to ultra-high risk (UHR) criteria, allowing for the detection of earlier stages of ARMS.[27,28] Yet, the importance of metacognition in early prodromal stages and the interaction with cognitive basic symptoms is still unclear.

Regarding neural correlates of metacognition and decision-making processes, several studies were conducted on healthy participants. The neural representation of uncertainty (risk or ambiguity) during decision-making was found to be represented in a frontal–striatal–thalamic network.[29,30] Blackwood and colleagues[31] applied the classical beads task and found the cerebellum and the parietal and occipital cortices to be involved. Furl and Averbeck[32] applied a modified version of the beads task for reward-related decision-making compared with a Bayesian model, and participants who completed the beads task drew fewer stimuli until decision. Furthermore, using an event-related design, the authors found increased activation in parietal, insular, anterior cingulate and striatal regions during decision-making in comparison to preceding draws. We recently developed a modified version of the beads task and found increased activation in the prefrontal–parietal executive functioning network as well as medial parietal–occipital regions and the cerebellum during the entire process of probabilistic reasoning in healthy volunteers. Furthermore, activity in the ventral tegmental area (VTA) and the ventral striatum (VS; comprising the nucleus accumbens) was detected during the final decision process.[33] Applying this task to patients with schizophrenia, a hypoactivation in the VTA and right VS during probabilistic decision-making was found, while the above-mentioned broad cortical activation pattern could be replicated.[34] Other authors assessing patients with schizophrenia also found differential activation patterns in frontal–striatal–thalamic regions during probabilistic learning or reward prediction tasks.[35–37]

Imaging techniques in general might be able to unravel the neurobiological alteration during ARMS. In a review, Wood and colleagues[38] concluded that an activation of the stress system and an increased striatal dopamine synthesis seem to be a marker of ARMS patients most at risk for later transition to psychosis, but huge variations in methodology must be noted. Several studies focused particularly on neuroanatomical abnormalities.[39–42] Other studies using positron emission tomography [^{18}F]-dopa have provided evidence for increased striatal dopamine activity in ARMS patients.[43] So far, to our knowledge, no functional assessments of VS functions during probabilistic decision-making in ARMS patients have been performed.

In view of the evidence for impaired metacognition as well as imaging findings in ARMS patients, and based on our findings in patients with schizophrenia suggesting reduced activation of the VS and VTA as neural correlates of altered decision-making, we hypothesized that we would find neural dysfunction in the VTA and right VS during probabilistic decision-making in patients already in the early stages of the disease. We applied a predescribed fMRI task[33,34] to ARMS patients and healthy controls to determine whether differential activation patterns in the VTA and VS can be identified, which might indicate a mechanism for the emergence of brief limited psychotic symptoms and disturbed cognition during prodromal states. Furthermore, we hypothesized that we would find an impaired capability to weigh information effectively along with a JTC bias, mirroring findings in patients with manifest illness.

Methods

Participants

The present study was approved by the local ethics committee of the Medical Faculty Mannheim of the University of Heidelberg. To be included in our study, patients had to fulfil the following predefined inclusion criteria: 1) attribution to ARMS according to the Early Recognition Inventory based on IRAOS (ERIraos),[28,44] defined as exceeding the cut-off (sum score ≥ 30) and/or presence of at least 2 cognitive basic symptoms and/or at least 1 APS and/or at least 1 BLIPS); 2) age between 18 and 40 years; 3) ability to provide written informed consent; and 4) sufficient German language skills. We excluded patients who fulfilled the criteria for FEP, substance dependence other than nicotine, or other disorders of the central nervous system requiring treatment. We excluded patients treated with antipsychotics; however, stable premedication with antidepressants was allowed. We included control participants matched for age, sex, level of education and premorbid verbal intelligence. Controls were required to have no family history of schizophrenia, bipolar disorder or suicide in first-degree relatives; no previous or current psychiatric disorders according to the Mini-International Neuropsychiatric Interview (MINI); and no previous or present psychopharmacological treatment.

Psychometric rating scales and neuropsychological characterization

Trained and certified clinicians characterized ARMS symptoms and general psychopathology using ERIraos,[28] the Positive And Negative Syndrome Scale (PANSS) and the

Psychotic Symptoms Rating Scale (PSYRATS). Further, we evaluated negative symptoms using the Scale for the Assessment of Negative Symptoms, comorbid depressive symptoms using the Calgary Depression Scale for Schizophrenia, general severity of illness using Clinical Global Impression (CGI) and psychosocial functioning using the Global Assessment of Functioning (GAF) and Personal and Social Performance scales. We applied the German versions of all scales, which were clinician-rated and validated in numerous previous investigations.

Neurocognitive domains were assessed using the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) consensus cognitive battery for schizophrenia,[45] containing working memory, verbal and visual learning, speed of processing, problem solving and vigilance measures. In addition, we assessed attention and executive functioning using the Trail Making Test, version B and the Wisconsin Card Sorting Test. Estimated premorbid verbal intelligence was assessed using the Multiple Choice Word Test, version B.

Classical beads task

The classical beads task[5] was administered on a laptop. Participants viewed beads of 2 colours being drawn out of a jar and had to decide from which of the 2 jars they were drawn (Fig. 1A). Colour ratios in the jars were 80%:20% or 20%:80%, respectively. After each draw, participants were asked if they were ready to decide which of the 2 jars the bead came from or if they preferred to view another bead. The maximum number of beads that could be viewed was 10. The task was not repeated, but consisted of a single run. The coloured beads were presented in a previously defined fashion (1-1-1-2-1-1-1-1-2-1). Afterwards, participants had to report how confident they were with their decisions (1 = totally uncertain, 2 = fairly uncertain, 3 = a little uncertain, 4 = a little certain, 5 = fairly certain, 6 = totally certain).

Modified beads task

We used a modified beads task fMRI paradigm, which is described elsewhere in more detail.[33] Briefly, participants viewed fish of 2 colours jumping out of 1 of 2 lakes and had to decide from which of the 2 lakes the fish came. Colour ratios in the lakes were 80%:20% or 20%:80%. After viewing each fish, participants were asked if they preferred to make a decision or view another fish. Fish were presented in a previously defined fashion, repeated 8 times with alternate starting points. After presentation of the selected number of fish, participants had to decide which lake the fish had come from and rate how confident they were with their decisions (1 = a little uncertain, 2 = fairly certain, 3 = very certain, 4 = totally certain). In the control condition, participants had to indicate the colour of the presented fish. Eight experimental blocks and 8 control blocks were presented. The duration of the whole experiment was 16.32 minutes (2.04 min for each of the 8 trials, consisting of 1 experimental block and 1 control block).

Functional MRI data acquisition, processing and analysis

Data were acquired on a 3 T Siemens Trio (Siemens Medical Systems) scanner using echo-planar imaging (28 axial slices, 4 mm thickness, 1 mm gap, repetition time 2000 ms, echo time 28 ms, field of view 19.2 cm, matrix 64×64).

We analyzed fMRI data using SPM8 (www.fil.ion.ucl.ac.uk/spm/software/spm8/), as described earlier.[33] First, data were preprocessed and a hybrid model was set up for first-level analysis, combining phasic and tonic aspects of the task, including 5 regressors of interest: last fish, all previous fish, each fish in the colour decision condition, duration of each lake decision block and duration of each colour decision block. Further regressors of no interest were entered to minimize error variance: decision and certainty ratings as well as 6 movement regressors derived from the realignment procedure. All regressors were convolved with the hemodynamic response function for model estimation.

The following linear combinations of the resulting β-weights were subjected to second-level random-effects analyses: last fish > all previous fish and lake decision > colour decision. We used 1-sample *t* tests to investigate differences between conditions and 2-sample *t* tests to analyze group differences.

For whole brain analyses, the significance threshold was set to $p < 0.05$, family-wise error (FWE)–corrected. For regions of interest (ROIs), the significance threshold was set to $p < 0.05$, small volume (SV)–corrected. Minimal cluster size threshold was set to k = 5 adjacent voxels. We selected the VS and VTA as ROIs. They were created with masks for region of interest analyses[46] according to an anatomic atlas.[47] The left VS mask contained 127 voxels, the right VS mask 93 voxels and the VTA mask 27 voxels.

Behavioural data analysis

To calculate the required sample size (assumed statistical power of 0.8, probability of a first order error $\alpha = 0.05$), we referred to the behavioural results of Broome and colleagues[23] and obtained a sufficient group size of $n = 21$.

We analyzed sociodemographic, psychometric and behavioural parameters using the SPSS software version 21.0 (IBM). We applied Student *t* tests and Fisher exact tests to investigate group-specific differences. Correlations were expressed using the Pearson correlation coefficient. Owing to the number of comparisons, we applied Bonferroni correction for multiple testing.

Results

We included 24 ARMS patients and 24 healthy controls in our final data analysis. A detailed definition of ARMS has been described previously.[28] There were no significant differences in age, sex, education and premorbid verbal intelligence between the groups (Table 1). Two patients had to be excluded from our analysis pertaining to the classical beads task because they were unable to adhere to the instructions. Patients were characterized as moderately affected according to PANSS, PSYRATS and ERIraos. The mean ERIraos sum score was 42.8.

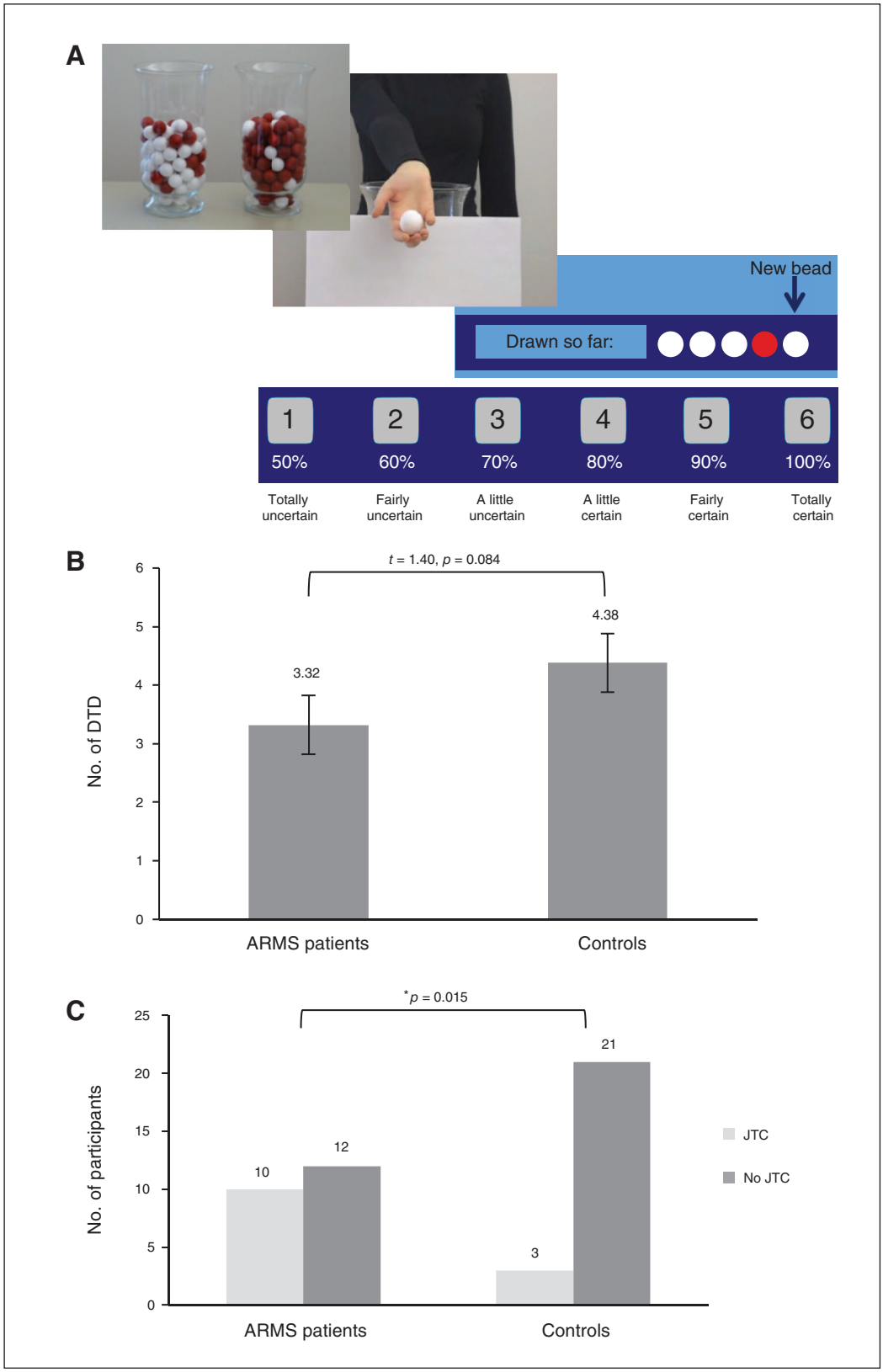

Fig. 1: (A) Illustration of the classical beads task. **(B)** Comparison of draws to decision (DTD) between patients in the at-risk mental state (ARMS) and controls. Results are reported as means and standard errors. **(C)** Comparison of jumping to conclusions bias (JTC; defined as 1 or 2 beads) between ARMS patients and controls (Fisher exact test, $p = 0.015$).

Some of the ARMS patients were taking antidepressants: citalopram ($n = 2$), mirtazapine ($n = 2$), sertraline ($n = 2$), paroxetine ($n = 1$) and trimipramine ($n = 1$). Owing to anxiety or agitation 2 patients were treated with low doses of lorazepam. We subdivided the ARMS group into patients in the early and late stages of ARMS; 6 patients presented at least 2 cognitive basic symptoms and/or exceeded the cut-off and were considered to be in the early stages of ARMS, and 18 patients presented APS and/or BLIPS and were considered to be in the late stages of ARMS (Table 1). The ARMS patients showed slight impairment in processing speed (Brief Assessment of Cognition in Schizophrenia symbol coding [BACS-SC]), working memory (letter–number sequencing [LNS]) and problem solving (Neuropsychological Assessment Battery — Mazes test) compared with healthy controls, but only the difference in problem solving withstood corrections for multiple testing (Table 2).

Classical beads task

The number of beads needed for decision (draws to decision [DTD]) differed between patients and controls (3.32 ± 2.68 v. 4.38 ± 2.43) on a trend level, as patients drew fewer beads to make a decision ($t_{44} = 1.40$, $p = 0.08$, 1-tailed; Fig. 1B). The mean level of certainty differed significantly in patients versus controls (4.32 ± 0.89 v. 4.96 ± 0.69, $t_{39.47} = 2.70$, $p = 0.010$), as controls were more secure in their decisions.

Significantly more patients than controls drew 1 or 2 beads to come to a decision (JTC 45.5% v. 12.5%, Fisher exact test, $p = 0.015$; Fig. 1C).

Modified beads task

The number of fish needed for decision (DTD) did not differ between patients and controls (4.70 ± 1.37 v. 4.83 ±1.37, $t_{46} = 0.34$, $p = 0.73$); the mean level of certainty was 2.76 ± 0.52 in patients and 3.15 ± 0.64 in controls ($t_{46} = 2.33$, $p = 0.024$). Comparing the number of participants showing JTC did not reveal any group differences.

General activation patterns on fMRI

Across-group comparisons

The comparison of the lake versus colour decision revealed significantly stronger brain activation for the lake condition in the frontal–striatal network (Table 3 and Fig. 2A). Moreover, ROI analyses revealed significantly increased activation for the lake decision in the VTA (Montreal Neurological Institute [MNI] coordinates: $x, y, z = –6, –16, –14$, k = 27, $t = 3.95$, $p = 0.002$,

Table 1: Sociodemographic and psychopathological characteristics of study participants

	Group, mean ± SD*		
Characteristic	ARMS, $n = 24$	Control, $n = 24$	p value
Age	22.0 ± 3.3	23.2 ± 4.3	0.28
Sex, female:male	10:14	9:15	0.52
Education level, yr	11.5 ± 1.6	11.8 ± 1.5	0.40
MWT-B	23.4 ± 4.2	24.3 ± 5.7	0.57
Estimated verbal IQ	94.8 ± 9.3	98.3 ± 14.4	0.32
ERIraos sum score	42.8 ± 14.8	—	—
ARMS, early:late	8:16	—	—
PANSS			
Total score	60.3 ± 12.9	—	—
Positive symptoms	13.2 ± 4.1	—	—
Negative symptoms	12.7 ± 4.8	—	—
Global psychopathology	34.5 ± 7.0	—	—
SANS	30.1 ± 20.1	—	—
CDSS	6.5 ± 4.6	—	—
PSP	61.7 ± 13.0	—	—
GAF	50.8 ± 8.8	—	—
CGI-S	4.0 ± 0.6	—	—
PSYRATS			
Amount of preoccupation	1.3 ± 1.5	—	—
Duration of preoccupation	1.5 ± 1.4	—	—
Conviction	1.4 ± 1.6	—	—
Amount of distress	1.8 ± 1.8	—	—
Intensity of distress	1.8 ± 1.7	—	—
Disruption	0.9 ± 1.2	—	—

ARMS = at-risk mental state; CDSS = Calgary Depression Scale for Schizophrenia; CGI-S = Clinical Global Impression — Severity; ERIraos = Early Recognition Inventory based on IRAOS; GAF = Global Assessment of Functioning; MWT-B = Multiple Choice Word Test (version B); 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; SD = standard deviation.
*Unless otherwise indicated.

Table 2: Neurocognitive characteristics of study participants

Characteristic	Group, mean ± SD		*p* value
	ARMS, *n* = 24	Controls, *n* = 24	
MATRICS test battery			
TMT-A, s	28.7 ± 8.3	26.1 ± 7.8	0.27
TMT-B, s	58.1 ± 18.2	53.0 ± 13.7	0.28
BACS-SC	57.7 ± 9.7	65.2 ± 10.4	0.013*
HVLT-R	28.8 ± 4.2	30.6 ± 4.6	0.17
WMS-III-SS	18.5 ± 3.7	20.0 ± 2.5	0.10
LNS	16.1 ± 2.9	17.9 ± 3.0	0.039*
NAB-Mazes	21.4 ± 3.6	24.0 ± 1.8	0.003
BVMT-R	29.3 ± 5.4	29.7 ± 4.7	0.78
Fluency	25.8 ± 6.6	26.0 ± 7.4	0.89
MSCEIT–Emotion management	91.4 ± 11.0	91.3 ± 7.8	0.98
MSCEIT–Social management	93.3 ± 7.4	92.4 ± 9.2	0.70
MSCEIT–Managing emotions	92.2 ± 8.3	91.6 ± 8.3	0.81
CPT-DPrime	2.4 ± 0.6	2.7 ± 0.6	0.14
WCST			
Categories completed	6.6 ± 1.2	6.8 ± 1.1	0.56
Total trials	78.4 ± 15.5	79.4 ± 11.1	0.79
Total errors (%)	19.6 ± 8.0	18.2 ± 6.0	0.47
Perseveration Score (%)	15.0 ± 13.1	13.2 ± 11.6	0.61
Concept perseverations	0.7 ± 1.0	0.4 ± 0.7	0.22
Failure to maintain set	0.9 ± 1.4	1.0 ± 1.5	0.77

ARMS = at-risk mental state; BACS-SC = Brief Assessment of Cognition in Schizophrenia — Symbol Coding; BVMT-R = Brief Visual Memory Test Revised; CPT = Continuous Performance Test; HVLT-R = Hopkins Verbal Learning Task Revised; LNS = letter-number sequencing; MATRICS = Measurement and Treatment Research to Improve Cognition in Schizophrenia; MSCEIT = Mayer–Salovey–Caruso Emotional Intelligence Test; NAB = Neuropsychological Assessment Battery; SD = standard deviation; TMT = Trail Making Test; WCST = Wisconsin Card Sorting Test; WMSIII-SS = Wechsler Memory Scale III — Spatial Span.
*Not significant after Bonferroni correction for multiple testing.

Table 3: Increased activation during the experimental (lake) decision compared to the control (colour) condition*

Activation	BA	k†	MNI†			Tmax§
			x	*y*	*z*	
Inferior parietal lobule	40	5288	36	–55	49	13.49
Superior parietal lobule	7	—	27	–67	52	13.11
Inferior parietal lobule	40	—	–36	–49	46	10.77
Inferior frontal gyrus	47	3024	33	20	–2	12.01
Cingulate gyrus	32	—	9	20	49	11.52
Middle frontal gyrus	11	—	27	50	–8	10.63
Middle frontal gyrus	—	289	–39	56	4	10.76
Inferior frontal gyrus	47	96	–30	23	–2	8.98
Inferior frontal gyrus	9	452	–45	8	31	8.79
Middle frontal gyrus	46	—	–51	29	31	6.72
Middle frontal gyrus	6	—	–30	–1	52	6.18
Cerebellum	—	22	0	–61	–38	5.96

BA = Brodmann area; MNI = Montreal Neurological Institute.
*Significance threshold set at $p < 0.05$, family-wise error–corrected.
†Coordinates of the peak voxel in the cluster.
‡Subcluster peaks are inserted.
§Maximal t value in the cluster.

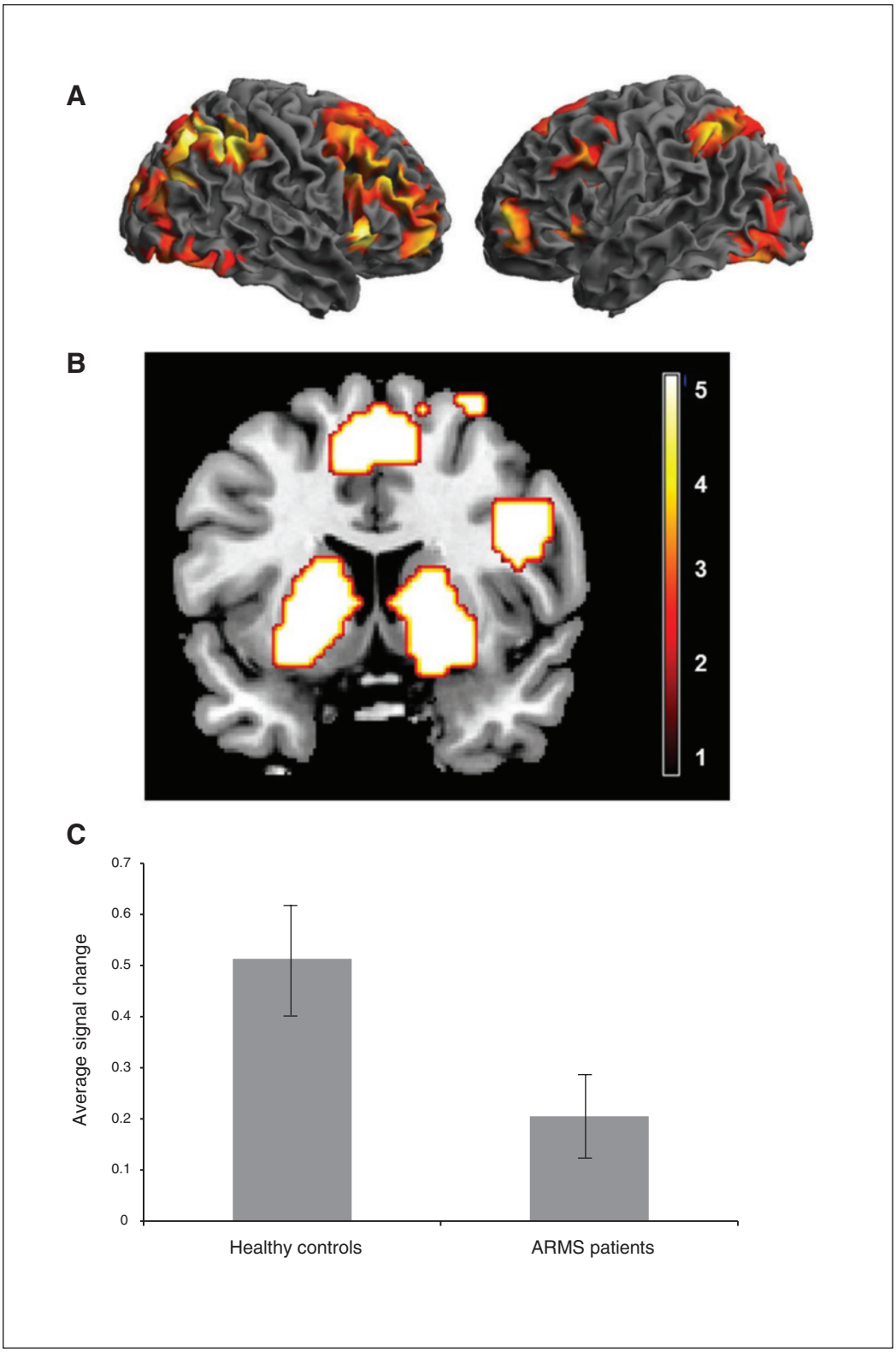

Fig. 2: (A) Main effect of the lake decision (lake decision > colour decision). Significance threshold is $p < 0.05$, family-wise error [FWE]–corrected. **(B)** Final decision-making, indicating enhanced activation for the last fish (last fish > all previous fish). Significance threshold set at $p < 0.05$, FWE-corrected. **(C)** Final decision-making, indicating average signal change for the last fish in comparison to all previous fish in the right ventral striatum. Displayed is the first Eigenvariate of the right ventral striatal activation extracted for a mask of the right nucleus accumbens, with a significance threshold set to 1. ARMS = at-risk mental state.

SV-corrected), and the VS bilaterally (left: $x, y, z = -15, 11, -2$, k = 11, $t = 3.06$, $p = 0.042$, SV-corrected; right: $x, y, z = 12, 11, -2$, k = 62, $t = 5.23$, $p < 0.001$).

When comparing the activation in response to the last fish versus all previous fish within the lake condition, significantly increased activation became evident mainly in the basal ganglia, midbrain, premotor and visual cortex. Accordingly, ROI analyses showed a significant effect in the VTA (MNI coordinates: $x, y, z = -6, -16, -11$, k = 27, $t = 7.36$, $p < 0.001$, SV-corrected) and in the VS bilaterally (left: $x, y, z = -18, 8, -2$, k = 88, $t = 7.63$, $p < 0.001$, SV-corrected; right: $x, y, z = 21, 8, -2$, k = 86, t = 8.06, $p < 0.001$; Table 4 and Fig. 2B).

Between-group comparisons

No group differences were revealed when applying whole brain analysis with FWE correction. However, ROI analyses showed a significant group difference in the right VS (coordinates: $x, y, z = 21, 17, -2$, k = 81, $t = 3.09$, $p = 0.030$) for the comparison of the last fish with all previous fish; we observed lower activation in ARMS patients (Fig. 2C). Because antidepressants (selective serotonin reuptake inhibitors) are known to affect blood oxygen level–dependent (BOLD) responses during cognitive task performance, we evaluated possible medication effects. A comparison of the BOLD responses in the ARMS subgroups with versus without antidepressant or anxiolytic medication revealed no group differences. Furthermore, as nicotine abuse could affect VS activation, we evaluated possible influences. We found no significant group differences in nicotine abuse or the number of cigarettes smoked per week. Moreover, no significant correlations between nicotine abuse and brain activation became apparent.

We found no differences in VTA activation between the groups.

Correlations between fMRI activation and psychopathology, behaviour and cognition

As a second-level analysis, we performed several exploratory correlations. In the patient group, severity of ARMS symptoms and other psychopathological measures did not correlate with the mean number of fish (modified beads task), the mean number of beads (classical beads task), or certainty at the time of decision.

Regarding associations with fMRI activation, the BOLD response did not correlate with the mean number of fish in the modified beads task or the mean number of beads in the classical beads task in patients or controls. However, we found significant inverse correlations between right VS activation and PANSS-negative score ($r = -0.465$, $p = 0.022$) and CGI severity score ($r = -0.409$, $p = 0.047$) as well as a significant positive correlation with the GAF score ($r = 0.415$, $p = 0.044$), but not with the ERIraos total score. No significant correlations between delusions, as observed using the PSYRATS or PANSS, and JTC performance or VS activation became apparent in our ARMS group.

Control participants showed a significant inverse correlation between the number of beads in the classical beads task and the MATRICS verbal fluency subtest (processing speed) ($r = -0.441$, $p = 0.031$). In ARMS patients, we observed a significant inverse correlation between the number of beads (classical beads task) and BACS-SC ($r = -0.431$, $p = 0.045$). We further observed a significant inverse correlation between left

Table 4: Increased activation during the final decision in comparison to all previous decisions in the lake condition*

			MNI†			
Activation	BA	k‡	*x*	*y*	*z*	Tmax§
Medial frontal gyrus	6	949	–9	2	58	8.59
Middle frontal gyrus	6		30	2	70	7.51
Medial frontal gyrus	6		6	11	52	7.19
Inferior frontal gyrus	47	1965	30	23	–2	8.35
Putamen			18	8	–2	8.34
Midbrain			–6	–28	–8	8.19
Lingual gyrus	17	803	9	–88	1	7.98
Lingual gyrus	17		–9	–88	1	7.56
Parahippocampal gyrus	19		30	–55	–8	7.42
Middle frontal gyrus	10	67	36	41	28	6.34
Precentral gyrus	6	41	–48	2	40	5.90
Parahippocampal gyrus	19	12	–27	–58	–5	5.85
Anterior cingulate	24	11	–9	32	19	5.48
Anterior cingulate	32		–12	29	28	5.16
Cerebellum		16	0	–34	–38	5.46
Postcentral gyrus	40	22	–45	–31	49	5.41
Postcentral gyrus	3		–42	–28	58	5.09

BA = Brodmann area; MNI = Montreal Neurological Institute.
*Significance threshold set at $p < 0.05$, family-wise error–corrected.
†Coordinates of the peak voxel in the cluster.
‡Subcluster peaks are inserted.
§Maximal t value in the cluster.

VS activation and LNS (r = –0.447, p = 0.028) in the patient group. These correlations regarding neurocognition, however, did not persist after correction for multiple testing.

Discussion

Assuming that altered activation patterns during probabilistic decision-making might occur early in the course of illness, we assessed neural activation during probabilistic reasoning in a sample of ARMS patients. In line with our hypothesis, ARMS patients displayed significantly reduced activation in the right VS during final decision-making.

On a behavioural level, we observed a significantly greater JTC bias in ARMS patients than controls in the classical beads task, replicating previous results.[22–24] After stratifying the patient group by early (n = 6) and late ARMS (n = 18), we did not find any significant differences regarding JTC (56.3% v. 16.7%, Fisher exact test, p = 0.12). Notably, we were unable to reproduce the JTC bias in the modified beads task (fMRI version). The unfamiliarity of the fMRI setting that was applied after the classical beads task might have affected the behavioural performance in this task. However, although this was an unexpected result, it allows us to interpret the differences in brain activation independent of behavioural differences, which would have led to differences in the number of presented trials between groups.

Regarding neural correlates, several imaging studies defined pathological findings with an early onset during the course of illness,[38] but important differences owing to the samples, ROIs, imaging techniques, methods of analysis and functional tasks used have to be noted. Focal grey matter volume reductions were described in several brain areas partially predicting the transition to psychosis.[39–41,48] Using fMRI, Yaakub and colleagues[49] observed hypoactivation in the left anterior insula during a working memory task in ARMS patients compared with healthy controls, but they found no significant differences in behavioural performance. In a study by Schmidt and colleagues,[50] abnormal frontoparietal connectivity during a working memory task became evident in an ARMS sample and was found to be related to the severity of psychiatric symptoms. Dandash and colleagues[51] proposed that ARMS is mediated by the interplay of alterations in dorsal and ventral corticostriatal systems. In contrast to these fMRI studies Howes and colleagues[43] used positron emission tomography [^{18}F]-dopa and observed a dopamine overactivity predominantly localized in the associative striatum in ARMS patients. Those findings emphasize the sensitivity of imaging techniques and, specifically, the importance of the VS in early stages of the disease.

In line with these studies, we observed a significant hypoactivation in the right VS during probabilistic decision-making in ARMS patients and could validate our previous findings in patients with schizophrenia.[34] We note that our results are constrained to ARMS without regard to pre-psychotic stages owing to the lack of transition data for our sample and to the generally low rates of psychotic transitions (22%) reported in the literature. However, our findings could indicate that alterations in the striatal system represent an early state in the development of psychosis.[38] In any case, they extend our knowledge of functional striatal abnormalities in ARMS and suggest a mechanism underlying brief psychotic and cognitive symptoms in this help-seeking group of participants. Our results further support proposals of a disturbed ability to propagate prediction errors in a hierarchical Bayesian inference framework between lower- and higher-level systems in patients with schizophrenia,[6,52–54] again extending them to ARMS.

We were not able to replicate the hypoactivation in the VTA that we had found in patients with schizophrenia, which could be interpreted as an effect of antipsychotic medication or chronicity of illness.

Although a significant correlation between right VS activation and PANSS-negative, GAF and CGI severity scores became evident, we did not find any correlations with neurocognitive domains in either ARMS patients or in healthy controls. In addition, the amount of neurocognitive impairment was rather low. In line with this assumption, we did not find differences in brain activation between groups in the block analysis, suggesting intact general probabilistic reasoning skills.

Our findings could indicate that a reduced activation of the VS is not simultaneously associated with marked neurocognitive impairment, but rather may represent an early cognitive phenomenon of upcoming psychotic syndromes.

On a functional level, these findings are compatible with a hierarchy of dysregulations in key dopaminergic regions already present in ARMS, even before marked neurocognitive impairments and psychotic symptoms become evident, and contribute to a neurocognitive theory of delusions. It should be re-emphasized, however, that we did not measure dopamine directly, that altered functions of the VS must not be exclusively attributed to disturbed neurotransmission of dopamine,[55] and that other neurotransmitter interpretations of our neurofunctional results are possible. Replicating neural alterations previously found in patients with schizophrenia in ARMS patients, without confounding effects of antipsychotic medication and duration of illness, suggests an early emergent mechanism underlying psychotic and cognitive features of ARMS. Our results highlight the importance of investigating possible neurobiological markers of disease risk by linking ARMS with structural or functional alterations using imaging studies. Longitudinal studies combining a sophisticated neurocognitive characterization with imaging techniques will further contribute to an improved knowledge about the pathological mechanism of psychosis. Furthermore, multimodal imaging studies that measure dopamine release or synthesis together with functional activation in ARMS would be desirable.

Limitations

Regarding several secondary end points, the sample size might have caused a reduction of power, limiting our ability to detect smaller effects, including correlations between fMRI activation and the mean number of fish in the modified beads task or the mean number of beads in the classical beads task; however,

according to our a priori power analysis, our study was sufficiently powered. As mentioned previously, when stratifying the patient group by early (n = 6) and late ARMS (n = 18), the observable difference regarding JTC (16.7% v. 56.3%) became nonsignificant, possibly because of the limited sample size.

Because we generally did not distinguish between early and late ARMS stages, the patient group might have been somewhat heterogeneous. Furthermore, according to the literature, only about 22% of ARMS patients will later transition to psychosis.[15–17] Therefore, we emphasize that our results are constrained to the neurobiology of risk constellations and cannot provide better insight into prepsychotic stages to be defined in a retrospective design. Large longitudinal studies will be necessary to further assess the association between altered brain functionality and transition to psychosis.

Furthermore, the fMRI setting of the modified beads task may have displayed an artificial and unfamiliar test condition, affecting behavioural performance but allowing for the detection of altered neural functions. Yaakub and colleagues[49] similarly found hypoactivation in the left anterior insula during a working memory task in ARMS patients without observing differences in behavioural performance.[49]

In general, forthcoming longitudinal studies should involve medication-naive FEP patients to further unravel the developmental process of meta- and neurocognitive deficits as well as underlying neuronal activation patterns.

Conclusions

To our knowledge, this is the first study assessing fMRI activation during probabilistic decision-making in ARMS patients, thus extending the insight into activation patterns. Compared with studies mainly focusing on behavioural data, the evaluation of fMRI might be more sensitive, more closely related to the primary cognitive processes and more independent of factors possibly confounding the behavioural phenotype. Using fMRI, we found hypoactivation in the right VS during final decision-making, mirroring effects observed in patients with schizophrenia, which suggests a dysregulated dopaminergic functioning leading to alterations in decision-making even before marked impairments in neurocognitive domains become evident. Further research is necessary to improve the pathogenic insight and to contribute to early cognitive interventions to counteract the development of delusions.

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