Schizophrenia Bulletin vol. 42 no. 6 pp. 1517–1527, 2016
doi:10.1093/schbul/sbw065
Advance Access publication May 17, 2016

Predictive Motor Timing and the Cerebellar Vermis in Schizophrenia: An fMRI Study

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Abnormalities in both time processing and dopamine (DA) neurotransmission have been observed in schizophrenia. Time processing seems to be linked to DA neurotransmission. The cognitive dysmetria hypothesis postulates that psychosis might be a manifestation of the loss of coordination of mental processes due to impaired timing. The objective of the present study was to analyze timing abilities and their corresponding functional neuroanatomy in schizophrenia. We performed a functional magnetic resonance imaging (fMRI) study using a predictive motor timing paradigm in 28 schizophrenia patients and 27 matched healthy controls (HC). The schizophrenia patients showed accelerated time processing compared to HC; the amount of the acceleration positively correlated with the degree of positive psychotic symptoms and negatively correlated with antipsychotic dose. This dysfunctional predictive timing was associated with BOLD signal activity alterations in several brain networks, especially those previously described as timing networks (basal ganglia, cerebellum, SMA, and insula) and reward networks (hippocampus, amygdala, and NAcc). BOLD signal activity in the cerebellar vermis was negatively associated with accelerated time processing. Several lines of evidence suggest a direct link between DA transmission and the cerebellar vermis that could explain their relevance for the neurobiology of schizophrenia.

Key words: predictive timing/cognitive dysmetria/schizophrenia/cerebellum/fMRI/dopamine

Introduction

Time is a fundamental dimension of physical reality. Our brains phylogenetically evolved within this reality and developed multiple neural systems to organize events in time. Four known brain systems are currently implicated in time processing. The hippocampal system subserves long-term memory, the chronological storing and recollection of events, and it is capable of dealing with very long time intervals.[1] The second system, located in the suprachiasmatic nucleus, is responsible for synchronizing various circadian and ultradian biorhythms to external conditions such as sunlight (the master pacemaker).[2] The third system is the cortico-striatal system, which is believed to be responsible for cognitively controlled interval timing (in the seconds-to-minutes range) and functions as a pacemaker-accumulator model (the cortex fires impulses that are accumulated in the striatum; the amount of accumulated impulses measures the amount of elapsed time).[3,4] The fourth system is the cerebellar system, which is believed to be implicated in automatic sub-second (millisecond) timing. For more on the neurobiology of time perception, see reviews.[5,6]

There is convincing evidence that time processing is impaired in schizophrenia. A recent meta-analysis[7] reviewed 24 studies from 1956 to 2015 and concluded that "results indicate that schizophrenia individuals are less accurate than healthy controls (HC) in estimating time duration across a wide range of tasks. Subgroup analyses showed that the fundamental timing deficit in schizophrenia is independent from the length of the to-be-timed duration (automatic and cognitively controlled timing) and from methods of stimuli estimation (perceptual and motor timing). Thus, time perception per se is disturbed in schizophrenia (not just task-specific timing processes) and this perturbation is independent from more generalized cognitive impairments". It has even been hypothesized that time-processing deficits might be one of the core underlying deficits behind schizophrenia.[8]

Specifically, timing impairments in the millisecond range might lead to discoordination of sensorimotor and mental processes, which could lead to higher-order symptoms of schizophrenia (a concept originally coined by Andreasen in the cognitive dysmetria theory[9,10]). This loss of fluidity and coordination in mental processes could manifest as psychosis.

Abnormalities in dopamine (DA) neurotransmission have long been considered to be involved in the pathophysiology of schizophrenia[11–13] and DA neurotransmission has been linked to changes in time processing. Numerous studies using DA receptor agonists (cocaine and methamphetamine) demonstrated acceleration of the "internal clock,"[14–16] while DA receptor antagonists (antipsychotics) demonstrated deceleration.[14,16] Experiments probing the effects of various neurotransmitter systems on time processing first demonstrated that there might be 2 time-processing systems in the human brain. One, the interval timing system (supra-second range), is dependent on working memory and is cognitively controlled, influenced by all drugs affecting the working memory; the other, the millisecond timing system, is automatic and influenced only by drugs manipulating the DA system.[17,18] Later on, lesions, TMS, and neuroimaging studies supported this notion and localized the interval timing system into the corticostriatal system, while the millisecond timing system was localized to the cerebellum.[6,19,20]

The present study investigates the neural substrate of time processing in schizophrenia using a predictive motor timing fMRI task.[21,22] It is a complex timing task requiring an accurate mental prediction about the future position of a target based on visual input as well as the precisely timed execution of a motor response. The task has been shown to robustly activate the cerebellum and the basal ganglia[22] and tests both millisecond timing (50–150 ms time window to execute the interception of the target, discrete movement timing) and interval timing (cognition-based mental prediction about a future position, continuous movement of the target). According to previous studies performed by Bareš[21,23] who investigated the predictive timing paradigm in patients with spinocerebellar ataxia (damaged cerebellum) and patients with Parkinson's disease (damaged basal ganglia), the cerebellar timing system seems to be more important during predictive motor timing than the cortico-striatal timing system. Given these results by Bareš and given the known literature about the involvement of the cerebellum in schizophrenia, we hypothesize that we will find major BOLD signal activity changes in the cerebellar timing system between the schizophrenia patients and controls.

Methods

Subjects

Altogether, 28 patients diagnosed with schizophrenia (32.0 ± 6.9 y, 6F + 22M) and 27 age-matched healthy controls (32.0 ± 6.3 y, 6F + 21M) participated in the study. All of the controls were recruited through advertising within the local community; they underwent an interview with a trained psychiatrist to rule out any psychiatric conditions, were right-handed, were native Czech speakers, had no history of mental illness or drug abuse and no brain disorder, and took no psychiatric medication. All of the patients were recruited from among schizophrenia inpatients of the University Hospital Brno, Czech Republic. The patients were diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) criteria using the Mini-International Neuropsychiatric Interview (MINI),[24] were right-handed and native Czech speakers. The clinical evaluation of the patients included the Positive and Negative Syndrome Scale (PANSS)[25] to rate the symptoms of schizophrenia; the Hamilton Anxiety Rating Scale (HAM-A)[26] to rate levels of anxiety; the Wechsler Adult Intelligence Scale (WAIS)[27] and Wisconsin Card Sorting Test (WCST)[28] to test for distinct aspects of cognitive functions; the International Cooperative Ataxia Rating Scale (ICARS)[29] to rate cerebellar symptoms; and the Simpson-Angus Extrapyramidal Side Effects Scale (SAS),[30] Abnormal Involuntary Movement Scale (AIMS),[31] and Barnes Akathisia Scale (BAS)[32] to rate the severity of extrapyramidal symptoms. All patients were treated with second-generation antipsychotics, mean antipsychotic dose was (719 ± 375) mg in CPZ equivalents; mean age (32.0 ± 6.9) years; mean illness duration (6.9 ± 6.8) years; mean number of previous psychotic episodes 2.78; and male/female ratio 22/6. The detailed characteristics of the schizophrenia patients are summarized in supplementary table 1. All participants signed an informed consent form. The study was approved by the local ethics committee at the University Hospital Brno.

The Interception Task

We used an interception task developed and previously published by one of the coauthors of this manuscript.[21] During the task, a target moved from left to right on a screen. The test subject was instructed to press a button to shoot a ball from the lower right corner of the screen to intercept the moving target. If the ball hit the target, an animation of an explosion was shown (supplementary figure 1). We varied the properties of the moving target in each trial. The target could move at 3 different speeds (slow, medium, and fast), at 3 different angles (0°, 15°, and 30°) and with 3 types of acceleration (no acceleration, acceleration, and deceleration). This gave $3 \times 3 \times 3 = 27$ trial types. The whole experiment consisted of 324 trials organized into 6 blocks with 54 trials each. Each trial type was thus presented 12 times. The blocks were separated by a 20-second pause. Within each block, the trials were presented randomly in an event-related design. During each trial, the trial characteristics as well as the subject

responses (reaction time, hit, early miss, or late miss) were logged. Each trial lasted an average of about 3.5 seconds, the length of the whole paradigm was about 20 minutes. The paradigm was programmed in E-prime (http://www.pstnet.com/eprime.cfm). The time window to hit the target, ie, the time period during which the button press led to a hit, was 50–175 ms, depending on the parameters of the moving target. Measured from the beginning of the trial, the time window between the earliest and the latest moment when a button press led to a hit was 500–2500 ms, again depending on the moving target parameters.

Image Acquisition Parameters

The scanning was performed using a 1.5 T Siemens Symphony scanner equipped with Numaris 4 System (MRease). Each functional run acquired 490 volumes (echo time [TE] = 35 ms, repetition time (TR) = 2300 ms, flip angle (FA) = 90°, 28 axial slices, slice thickness = 4 mm, in-plane resolution 220 × 178.8 mm, matrix size 64 × 52, voxel size 3.4375 × 3.4375 mm). Before each measurement, the paradigm was explained to the subjects, and they each performed one practice run consisting of one block of 54 trials.

Statistical Analysis of Behavioral Data

The behavioral data, consisting of trial characteristics such as the target speed, target acceleration, and target angle, and of subject performance such as reaction times and trial results, were obtained from the log files created during fMRI scanning. These data were analyzed with SPSS (SPSS Inc).

fMRI Data Analysis

Images were preprocessed using Statistical Parametric Mapping 8 (SPM-8) (http://www.fil.ion.ucl.ac.uk/spm). The preprocessing consisted of (1) correction for slice-timing differences, (2) alignment to mean image to correct for head motions, (3) normalization to a common stereotactic space (Montreal Neurological Institute template) using an affine transformation, and (4) smoothing using an isotropic 8-mm Gaussian kernel.

On the single-subject level (first-level analysis), a general linear model (GLM) with 3 regressors was created. The first regressor consisted of all hits (the intercepting ball hit the target), the second regressor of all early misses (the intercepting ball was shot too early), and the third regressor of all late misses (the intercepting ball was shot too late). The 6 motion parameters obtained during realignment and also the 5 time series extracted from 4 white matter and one CSF region of interest (ROI) were entered into the model as nuisance regressors. Four contrasts–HIT, MISS, HIT-MISS, and early MISS-late MISS–were defined using the regressors, and thus 4 contrast maps (maps of parameter estimates β) per subject were obtained.

On a group level (second-level analysis), the first-level contrast maps were evaluated using either 1-sample *t* tests (to show common activation across all 55 participants) or 2-sample *t* tests (to show group differences between the healthy controls and schizophrenia patients). The group-level analysis was done using the GLM-Flex Toolbox (http://mrtools.mgh.harvard.edu/index.php/Main_Page).

Results

Behavioral Results

The mean reaction times (time interval from the beginning of a trial to a button press) were 934.9 ± 35.7 ms in the schizophrenia group and 944.2 ± 22.1 ms in the control group ($P < .25$).

To test the hypothesis that schizophrenia patients have an accelerated time perception, we subdivided the misses into early misses (the intercepting ball passed before the target arrived) and late misses (the intercepting ball passed after the target arrived) and counted the overall number of hits (H), early misses (eM), and late misses (lM) for each subject. There was a significant group difference in the number of hits ($P < .001$) and early misses ($P < .001$), but not late misses ($P < .29$). The results are shown in figure 1.

We used partial correlation analysis to investigate the possible mechanisms responsible for this underestimation. The results are summarized in table 1. We found a significant ($P < .001$) correlation between accelerated time

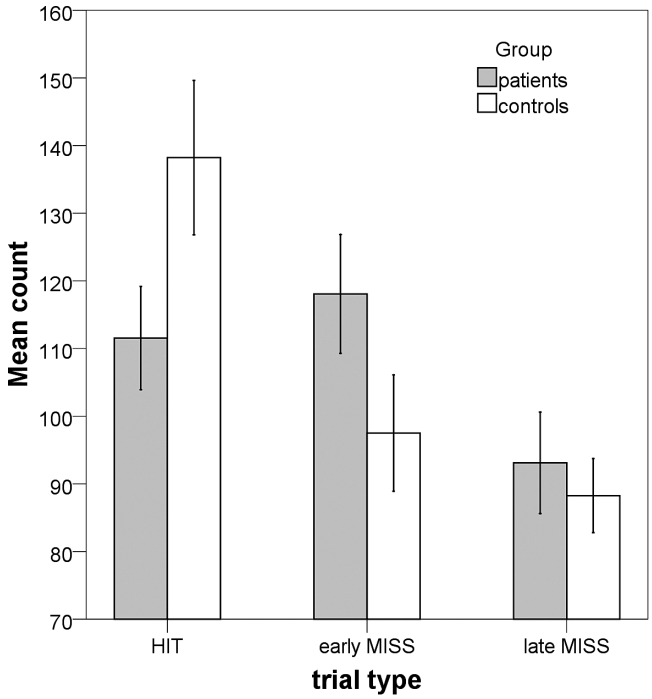

Fig. 1. Comparison of behavioral results of the 2 groups. The Box-and-Whisker bars represent the performance of subjects during the paradigm (the absolute count of hits, early misses, and late misses).

Table 1. Partial Correlation Coefficients (pCC) Showing the Association Between the Overall Number of Hits (H), Early Misses (eM), Late Misses (lM), and PANSS Subscales, Antipsychotic Doses (CPZ), ICARS Subscales, and Subscales of the Wechsler Adult Intelligence Test (WAIS) and Wisconsin Card Sorting Test (WCST)

	Variables Controlled For														
Correlated Variables	Age	Nr. EP	mRT	stdRT	CPZ	SAS	AIMS	BAS	HAMA	PANSS P	PANSS N	PANNS G	pCC	Significance	Remark
eM vs PP	●	●	●	●	●	●	●	●	●				**0.878**	**<.001**	Number of early misses
eM vs NP	●	●	●	●	●	●	●	●	●				0.184	.566	(accelerated time) correlates
eM vs GP	●	●	●	●	●	●	●	●	●				0.474	.120	with positive symptoms
eM vs CZP	●	●	●	●		●	●	●	●	●	●	●	**−0.879**	**.002**	(dopamine) and anticorrelates with antipsychotic doses (antidopaminergic)
H vs PP	●	●	●	●	●	●	●	●	●				−0.676	.022	Number of hits anticorrelates
H vs NP	●	●	●	●	●	●	●	●	●				−0.558	.075	with all PANSS subscales
H vs GP	●	●	●	●	●	●	●	●	●				−0.525	.097	and positively correlates with
H vs CPZ	●	●	●	●		●	●	●	●	●	●	●	0.643	.067	antipsychotic doses
lM vs PP	●	●	●	●	●	●	●	●	●				−0.522	.100	Number of late misses
lM vs NP	●	●	●	●	●	●	●	●	●				0.219	.518	significantly correlates with
lM vs GP	●	●	●	●	●	●	●	●	●				−0.181	.594	antipsychotic doses
lM vs CPZ	●	●	●	●		●	●	●	●	●	●	●	0.702	.035	
ICARS 1 vs eM	●	●	●	●	●	●	●	●	●				0.671	.215	No significant correlations
ICARS 2 vs eM	●	●	●	●	●	●	●	●	●				0.714	.176	
ICARS 3 vs eM	●	●	●	●	●	●	●	●	●				0.338	.578	
ICARS 4 vs eM	●	●	●	●	●	●	●	●	●				0.246	.689	
eM vs WAIS symbol search	●	●	●	●	●	●	●	●	●	●	●	●	−0.556	.195	Visual perception/analysis
eM vs WAIS similarities	●	●	●	●	●	●	●	●	●	●	●	●	0.065	.889	Abstract verbal reasoning
eM vs WAIS arithmetic	●	●	●	●	●	●	●	●	●	●	●	●	0.021	.965	Working memory
eM vs WAIS picture completion	●	●	●	●	●	●	●	●	●	●	●	●	−0.209	.602	Ability to quickly perceive visual details
eM vs WCST cc	●	●	●	●	●	●	●	●	●	●	●	●	0.417	.410	Executive function

Note: The dots represent variables that were controlled for during the partial correlation: mean reaction times (mRT) and standard deviations of reaction times (stdRT), age, number of psychotic episodes (Nr Ep), chlorpromazine equivalents (CPZ), PANSS positive symptoms subscale (PP), PANSS negative symptoms subscale (NP), PANSS general psychopathology subscale (GP), Simpson-Angus Extrapyramidal Side Effects Scale (SAS), Abnormal Involuntary Movement Scale (AIMS), Barnes Akathisia Scale (BAS), and Hamilton Anxiety Rating Scale (HAMA).

perception and positive symptoms of schizophrenia and a significant anticorrelation ($P < .001$) between accelerated time perception and antipsychotic medication doses; see table 1. We took care to exclude the effects of possible confounders, controlling the correlations for the effects of age, number of episodes, psychomotor speed (mean reaction times), extrapyramidal symptoms (BAS, AIMS, SAS), and overall level of anxiety (HAMA). We also investigated symptoms of ataxia measured by ICARS subscales (especially the ICARS IV subscale, measuring oculomotor deficits) and cognitive functions measured by selected subscales of the WAIS and WCST tests (working memory and executive function).

fMRI Results

This manuscript uses the following interpretation of hyper/hypoactivation: During the 1-sample *t* tests (schizophrenia+HC combined), hyperactivation means that the BOLD response in a given region was higher than baseline; hypoactivation means the opposite. During the 2-sample *t* tests, hyperactivation means that the BOLD signal was stronger in the schizophrenia group than in the control group; hypoactivation means the opposite.

Based on 3 trial types, HIT (H), early MISS (eM), and late MISS (lM), we defined 4 contrasts—HIT (H), MISS (eM+lM), HIT-MISS (2H-eM-lM), and early MISS-late MISS (eM-lM)—and used 1-sample *t* tests to identify the basic activations of each contrast across all 55 participants; see figure 2. Both the HIT and MISS contrasts "activated" regions in the brainstem (pontine nuclei and olive nucleus), extensive regions within the cerebellum (vermis3, vermis4, vermis5, vermis6, vermis7, vermis8, cerebellum6, cerebellum crus 1, and cerebellum crus 2), thalamus, basal ganglia (striatum), motor and premotor areas of the left side, and the supplementary motor area, and "hypoactivated" regions of the default mode network (DMN). In accordance with previously published results,[22] the paradigm thus extensively activated timing networks whose main components are the cerebellar and basal ganglia loops. The cerebellar hemispheres receive afferent projections from the brainstem nuclei (pontine-cerebellar tracts) which in turn receive projections from the cortex (cortico-pontine tracts). The cerebellar hemispheres project onto the deep cerebellar nuclei (DCN) in the vermis. The DCN project efferently onto the thalamus, which in turn projects back onto the cerebral cortex. Thus the closed cerebrum-cerebellum-cerebrum loops are formed.[33,34] The HIT and MISS contrasts had similar activations; the MISS activations were stronger (more statistically significant and more surviving thresholding). The HIT-MISS contrast demonstrated that during HITs, the basal ganglia and the cerebellar hemispheres are "hyperactivated," compared to MISSes. The eM-lM contrast showed "hypoactivations" of the brainstem regions and the basal ganglia during the early MISSes, although the statistical significance was very low ($P < .05$ uncorr.).

Because the MISS contrast delivered more statistically significant results than the HIT contrast, we used this contrast to investigate the group differences using 2-sample *t* tests. We found significant differences in brain activation between the schizophrenia group and healthy controls. The schizophrenia group had significant hypoactivations in the cerebellar vermis (vermis3, vermis6, vermis7, and vermis8), the basal ganglia (BG), and the supplementary motor area (SMA), and hyperactivations in the cerebellar hemispheres (lobulus6, crus1, and crus2), the default mode network, the amygdala, the hippocampus, and the nucleus accumbens bilaterally. The results are shown

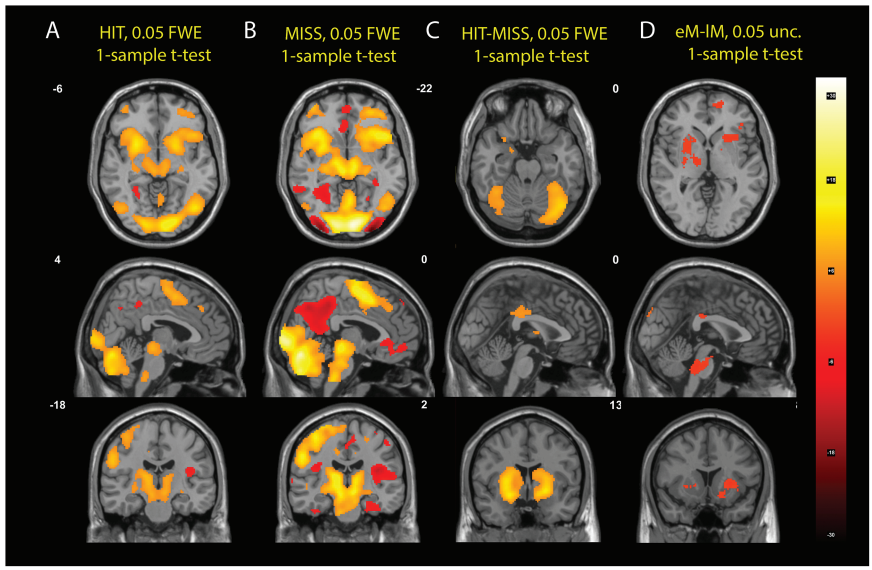

Fig. 2. Basic activations of the 4 contrasts computed using 1-sample *t* test across all 55 subjects. The (A) and (B) columns compare the activations for the HIT and MISS contrasts at the same Montreal Neurological Institute (MNI) coordinates. The (C) column shows the HIT-MISS contrast. The (D) column shows the difference in activations between the early MISS and late MISS regressors.

in figures 3A–C and listed in table 2. Figure 3D shows the correlation of the MISS regressor β-coefficients and the total number of early misses. Although the statistical significance is low (.05 unc.), the activation pattern shows relative hypoactivation of the cerebellar vermis in patients with high numbers of early misses, hinting at its role in the pathophysiology of accelerated timing. Supplementary figure 2 shows a group comparison of the parameter estimates (βs) for various ROIs for the MISS regressor.

Discussion

An analysis of both behavioral and neuroimaging data obtained during a predictive motor timing paradigm in schizophrenia patients and healthy controls resulted in 3 principal findings:

1. The schizophrenia patients demonstrated disturbed timing during a predictive motor timing paradigm. They had more early misses. The count of early misses was positively associated with the degree of positive psychotic symptoms as measured by PANSS and negatively associated with antipsychotic doses (CPZ equivalents). This result can reflect an accelerated time perception/timing in schizophrenia/psychosis.
2. This dysfunctional predictive timing was associated with alterations in several brain networks, especially those previously described as timing networks (basal ganglia, cerebellum, SMA, and insula), reward networks (hippocampus, amygdala, and NAcc), the DMN, and regions of the frontal, temporal and parietal lobes.
3. The count of early misses negatively correlated with the activation of the vermis within the schizophrenia group, ie, the more early misses a given schizophrenic patient had, the weaker the BOLD activity in the vermis. The vermis was the only region which anticorrelated with the BOLD signal activity.

Although our data show a distributed neuroanatomical pattern of regions involved in predictive motor timing in schizophrenia, the link between the performance in the task, the severity of psychosis, and the antipsychotic dose, and the relationship among all of that and the cerebellar vermis BOLD signal, suggest a prominent role of the cerebellar vermis in subinterval timing deficits in schizophrenia.

There is a wealth of literature describing the involvement of the cerebellar vermis in psychosis. A study conducted on a large sample of 1700 subjects demonstrated that 50% of the subjects who had functional psychosis had cerebellar vermal atrophy.[35] Reduced volume of the vermis is the most common cerebellar structural deficit reported in schizophrenia.[36] Post-mortem studies showed a reduced gyrification index in the cerebellar vermis in schizophrenia,[37] decreased neuronal integrity in the vermis in schizophrenia,[38] a reduced volume of the cerebellar vermis in neuroleptic-naive schizophrenia,[39] and a smaller cerebellar vermis, but not smaller hemisphere volumes, in patients with chronic schizophrenia.[40] These findings indicate that reduced/atrophic vermis/vermis hypoactivations are associated with psychosis, which is in agreement with our finding that the BOLD signal activity was reduced (hypoactive) in probands with schizophrenia. Additionally, we showed that the vermal BOLD activity negatively correlated with the number of early misses, ie, with timing. The number of early misses positively correlated with positive psychotic symptoms (psychosis) and negatively correlated with antipsychotic dose. These

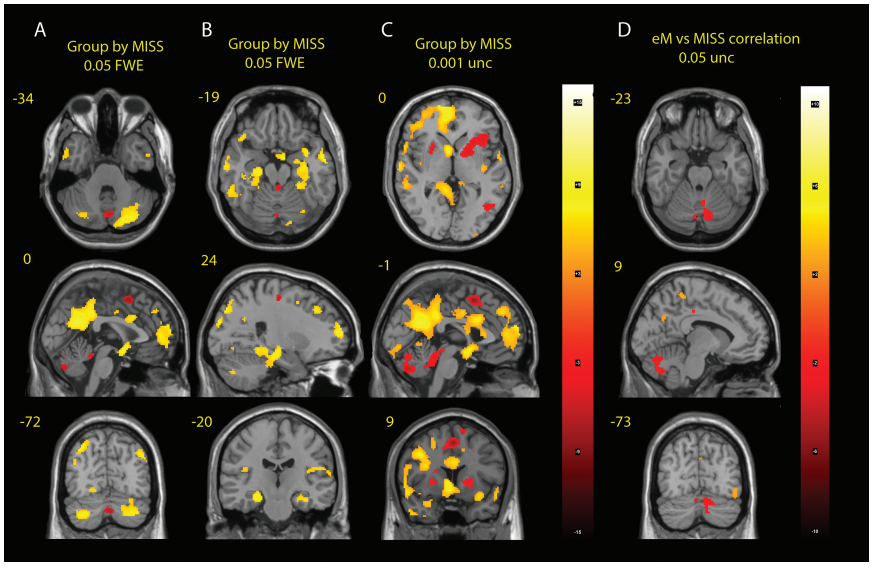

Fig. 3. Group differences in the MISS contrast (A), (B), (C) and the correlation of the frequency of early misses (eMs) with the MISS contrast (D).

Table 2. Overview of MISS Contrast Brain Activation Group Differences

			MNI Coordinates					
	Extent in Voxels	*t* Value	X	Y	Z	Side	Region Name	Remark
Timing networks	**71**	**−6.60**	**2**	**−74**	**−34**		**Cerebellum Vermis VII**	Structures known to be involved during timing paradigms in healthy controls. The cerebellar vermis contains the fastigial and dentate nuclei and is known as the "limbic cerebellum" with bilateral connections to dopaminergic regions (VTA, hippocampus, NAcc). Reduced vermis volume is the most common cerebellar structural deficit in schizophrenia
	36	**−5.71**	**0**	**−38**	**−18**		**Cerebellum Vermis I/II**	
	17	**−5.32**	**−2**	**−74**	**−18**		**Cerebellum Vermis VI**	
	1193	8.45	18	−82	−26	R	Cerebellum Crus I	
	1193	8.23	34	−77	−39	R	Cerebellum Crus II	
	1193	5.51	30	−70	−22	R	Cerebellum Crus VI	
	226	7.95	−32	−74	−39	L	Cerebellum Crus II	
	131	**−8.51**	**2**	**10**	**52**	**R**	**Supplementary Motor Area**	
	37	**−5.27**	**12**	**8**	**68**	**R**	**Supplementary Motor Area**	
	15	**−5.29**	**−15**	**−6**	**57**	**L**	**Supplementary Motor Area**	
	168	**−4.82**	**22**	**12**	**2**	**R**	**Putamen**	
	41	**−5.60**	**18**	**6**	**1**	**R**	**Putamen/Pallidum**	
Limbic structures	4609	6.36	−42	−26	−14	L	hippocampus	All limbic and reward processing structures hyperactivate in schizophrenia compared to controls; at the same time, all these structures are part of the dopaminergic mesolimbic pathway
	4609	8.15	−25	−19	−17	L	Hippocampus	
	632	6.53	29	−14	−18	R	Hippocampus	
	4609	6.64	−26	−32	−12	L	Parahippocampal Gyrus	
	632	6.51	24	−6	−18	R	Amygdala	
	481	7.39	0	2	−13		Nucleus Accumbens/ olfactory tubercle	
	208	6.96	2	14	30	R	Anterior Cingulate Cortex	
Default Mode Network	4609	9.66	−2	−56	24	L	Precuneus	DMN is known to fail to deactivate in schizophrenia, hence the relative hyperactivation in schizophrenia patients compared to controls
	4609	7.81	12	−53	31	R	Precuneus	
	4609	9.62	8	−38	32	R	Posterior Cingulate Cortex	
	4609	8.31	−5	−41	43	L	Middle Cingulate Cortex	
	343	8.85	−64	−10	−12	R	Middle Temporal Gyrus	
	159	7.64	56	0	−18	L	Middle Temporal Gyrus	
	1680	9.73	−8	52	6	L	Superior Frontal Gyrus—Medial Part	
	135	6.3	4	44	38	R	Superior Frontal Gyrus—Medial Part	
	1099	7.8	−36	−71	46	L	Angular Gyrus	
	288	6.8	42	−72	36	R	Angular Gyrus	
Motor regions	854	6.21	−53	1	22	L	Precentral Gyrus	motor cortices, button pressing
	854	6.02	−50	−11	35	L	Postcentral Gyrus	
	602	7.37	58	−6	16	R	Postcentral Gyrus	
	132	7.28	27	−27	53	R	Precentral Gyrus	
Insula	103	6.04	−40	−4	−10	L	Insula	interoceptive awareness, known to be involved in hallucinations in schizophrenia
	632	8.02	36	4	−14	R	Insula	
	168	**−6.64**	**26**	**20**	**6**	**R**	**Insula**	
	168	**−4.81**	**38**	**16**	**2**	**R**	**Insula**	
	602	7.24	43	−11	24	R	Rolandic Operculum	
	854	7.64	−46	−10	22	L	Rolandic Operculum	
Fusiform	4609	6.34	−23	−41	−11	L	Fusiform Gyrus	face recognition
	632	7.01	26	−36	−22	R	Fusiform Gyrus	
	118	7.38	38	−48	−24	R	Fusiform Gyrus	

Table 2. *Continued*

	Extent in Voxels	*t* Value	MNI Coordinates X	Y	Z	Side	Region Name	Remark
Frontal	1680	9.01	−26	58	12	L	Superior Frontal Gyrus	
	91	7.76	−22	32	38	L	Superior Frontal Gyrus	
	37	**−5.82**	**12**	**0**	**72**	**R**	**Superior Frontal Gyrus**	
	854	7.46	−40	10	38	L	Middle Frontal Gyrus	
	29	**−5.79**	**40**	**38**	**30**	**R**	**Middle Frontal Gyrus**	
	7	**−5.06**	**27**	**−2**	**56**	**R**	**Middle Frontal Gyrus**	
	588	6.93	−50	34	8	L	Inferior Frontal Gyrus—pars triangulars	
	588	6.34	−43	30	−12	L	Inferior Frontal Gyrus—pars orbitalis	
	168	**−5.98**	**40**	**24**	**−2**	**R**	**Inferior Frontal Gyrus—pars triangulars**	
	1680	10.12	−12	62	−2	L	Medial Surface of the Frontal Lobe—Orbital Part	
Occipital	1099	8.85	−32	−86	24	L	Middle Occipital Gyrus	
	1099	7.43	−43	−65	25	L	Middle Occipital Gyrus	
	100	7.53	24	−90	34	R	Superior Occipital Gyrus	
	68	7.85	12	−102	10	R	Superior Occipital Gyrus	
	18	**−5.91**	**40**	**−64**	**4**	**R**	**Middle Occipital Gyrus**	
	7	**−5.19**	**36**	**−72**	**22**	**R**	**Middle Occipital Gyrus**	
Pariet	**6**	**−5.29**	**−30**	**−56**	**52**	**L**	**Inferior Parietal Lobule**	
	23	**−5.43**	**53**	**−37**	**34**	**R**	**SupraMarginal Gyrus**	
Temp	588	6.28	−57	12	−11	L	Superior Temporal Pole	
	22	6.35	36	24	−24	R	Superior Temporal Pole	

Note: MNI, Montreal Neurological Institute. All regions surviving the whole-brain 0.05 FWE multiple comparisons correcture are shown ($P < 1.67 \times 10^{-6}$). Bold shows hypoactivations and unbold shows hyperactivations in schizophrenia subjects compared to controls.

results may offer indirect support for the cognitive dysmetria hypothesis.

Our data suggest a link between time processing (as measured by the number of early misses) and DA neurotransmission. The evidence is provided by the opposing effects of antipsychotic medication (DA receptor antagonists) and positive psychotic symptoms (that may reflect DA hyperactivity) on the number of early misses.

Several lines of evidence suggest a link between the DA system, the cerebellar vermis, and the millisecond timing that may explain our pattern of findings. A seminal study investigating dopaminergic innervation of the cerebellum conducted on primates using immunohistochemistry methods[41] found that "axons immunoreactive for the DA membrane transporter, a specific marker of DA axons, were present in high density, but only in certain lobules of the cerebellar vermis". A later study confirmed the result.[42] Indirect but striking evidence comes from a vast body of literature linking the cerebellar vermis to several psychiatric disorders with the involvement of DA neurotransmission and treated with dopaminergic drugs. Several morphometric studies demonstrated cerebellar vermis reductions in bipolar disorder patients[43–45] and subsequent reductions with every bipolar episode. Several studies have shown a reduced vermis in ADHD, a disorder linked to DA abnormalities and treated with psychostimulant dopaminergic drugs.[46–48] Children treated with methylphenidate had larger vermi than drug-naive children.[47,48] There is evidence linking the cerebellar vermis to stimulant addiction.[49] However, it seems unclear in which direction the causality between the vermis and disturbed DA neurotransmission goes. Neuroanatomical studies of vermal connectivity have shown that connections with the dopaminergic areas in the brainstem—the ventral tegmental area (VTA)—go both ways. Fluorescent retrograde double-labeling in rats has shown that VTA projects to the cerebellum.[50] Other histologic staining studies have demonstrated that vermal Purkynje cells project directly and indirectly to the VTA and the substantia nigra.[51,52] Snider demonstrated that artificial lesions on the vermis in rats led to altered DA metabolism in the forebrain,[53] which would suggest a primary role of the vermis. Other experiments demonstrated that dopaminergic drugs can influence millisecond timing.[14,15,17]

The link between aberrant DA neurotransmission in schizophrenia and the cerebellar vermis functioning might be an alternative explanation of the cognitive dysmetria hypothesis—or it may complement the possibility of abnormal wiring within the cortico-thalamo-cerebello-cortical loops.[9] The link is provided by the following chain of arguments: aberrant DA neurotransmission in schizophrenia influences the cerebellar vermis. The vermis is implicated in millisecond timing across many domains of motor, perceptual, and cognitive tasks. Disturbed millisecond timing leads to discoordination and a loss of fluency in mental processes, which manifests as psychosis. The cognitive dysmetria hypothesis is based on an analogy with motor dysmetria. Several experiments with cerebellar patients demonstrated that disturbed timing in sequential muscle contractions of agonists and antagonists leads to discoordination and thus dysmetria, which leads to a loss of tracking accuracy and creates disjointed responses.[54] The best examples are provided by ball-throwing experiments,[55,56] by paced finger-tapping tasks,[57] and by dysdiadochokinesis in cerebellar patients. Mauk looked at the relationship between timing, coordination, and learning.[58] Specifically relating to vermis, one study[59] found that transcranial magnetic stimulation of the cerebellar vermis caused timing dysfunctions. Accumulating evidence has demonstrated that the cerebellum is involved not only in motor control and coordination,[60] but also in perception[34] and cognition.[61,62] This is further corroborated by the anatomical connections of the cerebellum, which is connected to motor areas as well as to limbic regions and the frontal cortices.[33,63,64] Interestingly, many motor deficits commonly observed in cerebellar patients are observed in schizophrenia.[36]

To keep this manuscript focused and short, we moved our discussion of other brain activations to supplementary material. Of interest are the altered activations in the reward circuitry (hippocampus, amygdala, and ncl. accumbens) of the schizophrenia patients, because all these regions are projection sites of the dopaminergic neurons in the VTA.

Limitations

The study was performed on older fMRI hardware with a resolution of 1.5T. The resolution was insufficient for differentiating the individual structures within the vermis, ie, differentiating the individual cerebellar nuclei.

All of the patients were on long-term antipsychotic medication, which may have influenced their test performances. Because the effect of medication can be manifested by extra-pyramidal symptoms and a potential sedative effect, we would expect a higher count of late misses and slower reaction times. Quite contrary to that, we saw the opposite effect—antipsychotic medication tended to normalize the timing performance. Furthermore, we controlled for the medication effects in our analyses by measuring the EPS (BAS, AIMS, and SAS scales) and the total daily antipsychotic doses (CPZ equivalents), and we included those as covariates wherever possible. We did not observe any effect of the EPS on the task performance, neither did we observe any prolongation of reaction times; we observed the opposite: early misses were more frequent and reaction times were shorter in the schizophrenia group.

Supplementary Material

Supplementary material is available at http://schizophreniabulletin.oxfordjournals.org.

Funding

Ministry of Health of the Czech Republic (15-31063A).

Acknowledgment

The authors have declared that there are no conflicts of interest in relation to the subject of this study.

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