Effects of rhythmic auditory stimulation on upper-limb movement speed in patients with schizophrenia spectrum disorders

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Acknowledgments

Not applicable

Author contributions

SMW contributed to conceptualization, methodology, and data analysis. CYL contributed to methodology and data analysis. THYT, HLC, CHL, THN, CKT, WMW, and SHWC contributed to methodology and data collection. All authors contributed to manuscript writing and reviewing.

Abstract

Objective. Movement slowness, linked to dysfunctional basal ganglia and cerebellum, is prevalent but lacks effective therapy in patients with schizophrenia spectrum disorders. This study was to examine immediate effects of rhythmic auditory stimulation (RAS) on upper-limb movement speed in patients.

Methods. Thirty patients and 30 psychiatrically healthy people executed the right-hand task and the both-hand task of the Purdue Pegboard Test when listening to RAS with two tempi: normal (equal to the fastest movement tempo for each participant without RAS) and fast (120% of the normal tempo). The testing order of the RAS tempi for each participant was randomized.

Results. Patients had lower scores of right-hand and both-hand tasks than did psychiatrically healthy people. Scores of right-hand and both-hand tasks were higher in the fast-RAS condition than the normal-RAS condition in participants.

Conclusions. This is the first study to explore the possibility of applying RAS to movement therapy for patients with schizophrenia spectrum disorders. The results demonstrated that faster RAS was effective in inducing faster upper-limb movements in patients and psychiatrically healthy people, suggesting that manipulating RAS may be a feasible therapeutic strategy utilized to regulate movement speed. The RAS may involve alternative neural pathways to modulate movement speed and thus to compensate for impaired function of basal ganglia and cerebellum in patients.

Keywords: rhythmic auditory stimulation; auditory cue; upper limb movement; schizophrenia

Introduction

Schizophrenia is a devastating and costly neuropsychiatric disease. The symptoms are complicated, encompassing positive symptoms (e.g., perceptual and thought distortion), negative symptoms (e.g., reduced motivation and social interaction), cognitive impairments, and motor abnormalities [1,2]. The impact of these tricky symptoms is large, including the dramatic reduction of productivity in patients and the heavy cost of medical care in the society [3]. Schizophrenia has been ranked as one of the most severe diseases leading to heavy global burdens [3]. Finding how to effectively alleviate the symptoms and improve function in schizophrenia patients is of critical importance to the current healthcare.

Motor abnormalities, such as motor slowness (i.e., bradykinesia), are prevalent in patients with schizophrenia spectrum disorders [4], but lack specialized and effective treatment in the present medical care. About 80% of chronic patients under long-term healthcare still suffer from motor problems [4], the prevalence of which is much higher than that (around one third) of residual positive symptoms [5]. One possible reason for the loss of treatment focus on motor problems is that traditionally motor abnormalities are considered by-products of antipsychotic medications [6]. However, this traditional notion has been overridden by the current evidence showing that aberrant movements have existed in drug-naïve schizophrenia patients [7], meaning that motor abnormalities are associated with the illness itself and may be worsened by antipsychotics afterwards [7]. Moreover, research has suggested that the motor impairments in patients are linked to dysfunctional basal ganglia [7-11] and cerebellum [10-12], both of which play crucial roles in the pathoetiology of schizophrenia [8,12,13]. Therefore, motor abnormalities have been emphasized to be a cardinal symptom in patients with schizophrenia spectrum disorders [14,15]. Developing effective therapy for motor abnormalities in patients is urgently needed in order to fill up the current treatment gap.

The use of rhythmic auditory stimulation (RAS) has been proved to be an effective therapeutic strategy for alleviating bradykinesia resulting from aberrant basal ganglia [16-19]. A typical motor training session associated with RAS requires patients to perform a repetitive movement (e.g., walk) and match the movement pace to the tempo of the metronome sound or music, which could be gradually increased [18,19]. Before the training, in order to understand the performance level in each patient, the movement pace without the aid of RAS (“baseline tempo”) is measured [18,19]. In an actual training session, therapists will initially provide RAS with a tempo equal to 100% of the baseline tempo (“normal tempo”) for each patient, gradually increase the RAS tempo, and ultimately provide

RAS with a tempo of 120% of the baseline tempo ("fast tempo") [18,19]. Several training sessions could be involved in one week. With each training week, both of the normal and fast tempi in one training session could be increased by 10% [18,19]. It has been found that humans have neural connections between auditory and motor brain areas, such as cerebello-cortical neural circuits and direct neural projections from auditory to motor brain regions [20], which explains human innate synchronization of movement rhythm to the regular beat of sounds from the environment [17,18,20]. Because of this human neuroanatomical network [20], providing RAS is a feasible way used to provide the timing template generated from the environment for human movements and regulate human movement speed [17,18,20]. It has been suggested [11,21-24] that aberrant basal ganglia and cerebellum cause a failure of timing control over movement execution and thus are linked to bradykinesia. In the case of patients with such brain dysfunction, providing RAS remains promising for regulating movement speed because it may still activate neural pathways that are alternatives to those of basal ganglia or cerebellum [17,18,20] given rich neural connections between auditory and motor brain regions [20]. For patients with impaired basal ganglia, providing RAS has been demonstrated to be effective in alleviating bradykinesia [16,18,19]. However, it is surprising that earlier studies mainly examined responses of lower-limb movements, such as gait [16,18,19], but not those of upper-limb movements to RAS although upper-limb movement training also needs practice and repetition of movements. In addition, to our best knowledge, no studies have examined effects of RAS on movements in patients with schizophrenia spectrum disorders, who have impaired basal ganglia and cerebellum [8,12,13]. In schizophrenia, research [23] has shown that another type of sensory stimulation (i.e., visual motion cueing) is useful in modulating speed of upper-limb movements. Given the review papers [16,25] reporting that more evidence supports positive effects of auditory cueing on movement speed than those of visual cueing in patients with aberrant basal ganglia, it is valuable to examine effects of RAS on speed of upper-limb movements in patients with schizophrenia spectrum disorders. The results will add new evidence of valid movement therapy for patients.

To sum up, the purpose of this study was to examine immediate effects of RAS on speed of upper-limb movements in patients with schizophrenia spectrum disorders. The hypothesis was that RAS with the fast tempo, which was 120% of the baseline tempo, induced faster upper-limb movements than did RAS with the normal tempo, which was 100% of the baseline tempo. In order to gain a complete understanding of effects of RAS on different types of upper-limb movements, one-hand (right-hand) and both-hand movement tasks were involved in this study when RAS effects were tested.

Methods

Study design

This study used a 2 × 2 mixed design with one between factor (group: patients versus psychiatrically healthy people) and one within factor (RAS: normal RAS versus fast RAS). After the measurement of the baseline tempo, each participant was randomly assigned to a normal-fast or fast-normal RAS sequence. Speed of the upper-limb movements was assessed when participants received the normal RAS and the fast RAS. In addition, although the task (right-hand versus both-hand) was not the factor of our major interest, each participant was also randomly assigned to a right-both or both-right hand task sequence.

Participants

Patients were recruited from community rehabilitation centers. They were included if (a) they were diagnosed with schizophrenia or schizoaffective disorder and without any other psychiatric diseases confirmed by psychiatrists according to the Diagnostic and Statistical Manual of Mental Disorders- Fifth Edition [26]; (b) they were right-handed, which was checked by self-report; (c) they were 18 years old or above; and (d) they had no neurological or musculoskeletal problems that affected upper-limb movements. Psychiatrically healthy people were recruited from the university and communities. Their inclusion criteria were absence of psychiatric diseases by self-report and aforementioned (b) to (d).

The assessment of upper-limb movements: The Purdue Pegboard Test

The Purdue Pegboard Test includes the right-hand task, left-hand task, both-hand task, and assembly task [27]. This study adopted the right-hand task and the both-hand task considering the research interest in unimanual and bimanual movements in participants with right-handedness. The pegboard has pins in the upper-right and upper-left cups and has two vertical rows of holes near the midline of the board. For *the right-hand task*, the examinee was required to use the right hand to pick one pin per time from the upper-right cup and insert each pin to a hole in the right row top to bottom as quickly as possible within 30 seconds. If a pin drops off the hand during the test, the examinee was required to simply ignore it and pick a new pin from the cup immediately. Before the testing, the examinee was allowed to insert three pins for practice. In the formal testing, the task score is the number of pins inserted in holes within 30 seconds. In this study, the average task score for three trials was used to reflect speed of the right-hand movement.

For *the both-hand task*, the examinee was required to use the right hand to pick one pin per time from the upper-right cup and insert each pin to a hole in the right row, as well as use the left hand to pick one pin per time from the upper-left cup and inset each pin to a hole in the left row simultaneously. The examinee was required to execute the task as quickly as possible within 30 seconds. Before the testing, the examinee was allowed to insert three pin pairs for practice. In the formal testing, the task score is the number of pin pairs inserted in holes within 30 seconds. The average task score for three trials was used to reflect speed of the both-hand movement. The Purdue Pegboard Test has great test-retest reliability for the three-trial administration (Right hand task: ICC = 0.82; both hand task: ICC = 0.85) [28] as well as satisfactory content and construct validity [29].

Procedure

After giving informed consent, each participant was randomly assigned to either do the right-hand task first or the both-hand task first and then do the other task second. After receiving the task sequence, each participant was further randomly assigned to either do the normal-RAS condition first or the fast-RAS condition first and then do the other condition second. The experiments were conducted in a quiet room. For each movement task, the participant executed the movement task without RAS first to ascertain his/her baseline task score, which was used to calculate *the baseline tempo* (the task score multiplied by two; unit: the number of pins/pin pairs per minute). The participant then executed the movement task when listening to the rhythmic beep sound with a tempo being 100% of the baseline tempo ("*normal tempo*") first, or with a tempo being 120% of the baseline tempo ("*fast tempo*") first according to the assigned RAS sequence. The participant was encouraged to insert a pin/pins to a hole/holes when hearing the beep sound during the right-hand task and the both-hand task. The rhythmic beep sound, which serves as RAS, was generated and adjusted by the Mac computer application- "QuickNome". For each movement task, three trials under the baseline (no-RAS) condition and each RAS condition were required. The mean score of three trials was calculated.

Statistical analysis

The two-way repeated measures analysis of covariance (ANCOVA) was used to examine group differences (patients versus psychiatrically healthy people) and effects of RAS (baseline/no-RAS versus normal RAS versus fast RAS) after controlling effects of covariates. The dependent variables were the right-hand task score and the both-hand task score. The alpha level (two-tailed) was set at 0.05. The effect size η^2 was calculated. Large, medium, and small effect sizes are η^2=0.14, η^2=0.06, and η^2=0.01, respectively [30].

Results

Demographic data

A total of 30 patients and 30 psychiatrically healthy people were recruited (Table 1). Five patients (16.67%) were on risperidone. Three patients (10.00%) were on olanzapine. Two patients (6.67%) were on each of the following antipsychotics: amisulpride, clozapine, and trifluoperazine. One patient (3.33%) was on each of the following antipsychotics: aripiprazole, haloperidol, quetiapine, sulpiride, and zuclopenthixol. One patient (3.33%) was on each of the following combinations: aripiprazole/paliperidone, aripiprazole/clozapine, amisulpride/olanzapine, amisulpride/risperidone, clozapine/paliperidone, and clozapine/zuclopenthixol. Medication data of five patients were missing. Significant differences between patients and psychiatrically healthy people were found in age and education.

Group differences

The two-way ANCOVA was conducted to control confounding effects of age, education, and the gender ratio on the right-hand task score and the both-hand task score (Table 2 and Fig. 1). No interaction between groups (patients and psychiatrically healthy people) and conditions (baseline/no-RAS, normal RAS, and fast RAS) was found in the right-hand task score (P=0.721) and in the both-hand task score (P=0.910). Group differences were found in the right-hand task score and in the both-hand task. Patients had lower scores on the right-hand task and the both-hand task than did psychiatrically healthy people.

Effects of RAS

Condition effects were found in the right-hand task score and in the both-hand task score. Scores of the right-hand task and the both-hand task were higher in the fast RAS condition than the baseline/no-RAS condition, and then in the baseline/no-RAS condition than the normal RAS condition.

Additional analyses

In order to provide additional information of the task effect and also increase homogeneity of the patient group, we conducted extra three-way ANCOVA to examine group differences (28 patients diagnosed with schizophrenia versus 30 psychiatrically healthy people), effects of RAS, and effects of the task (right-hand versus both-hand) on scores after controlling confounding effects of age, education, and the gender ratio (Table 3). No three-way or two-way interactions were found (P=0.100 to 0.804). Group differences, RAS effects, and task effects

were found. Results of group differences and RAS effects were similar to those of the previous two-way ANCOVA. In addition, scores of the right-hand task were higher than those of the both-hand task.

In addition, we specifically targeted 28 patients diagnosed with schizophrenia to conduct two-way ANCOVA (main effects: RAS and the task; covariates: age, education, and gender). No interaction (P=0.386) and no task effect (F[1,24]=3.55; P=0.072; η^2=0.13) were found. Nevertheless, RAS effects remained significant (F[2,48]=4.42; P=0.017; η^2=0.16). Post hoc tests with the Bonferroni correction for multiple comparisons showed that scores were higher in the fast RAS condition than the normal RAS condition, and higher in the baseline/no-RAS condition than the normal RAS condition. The difference in scores between the fast RAS condition and the baseline/no-RAS condition became non-significant, which may be due to the reduced total sample size (n=58 versus n=28). We further conducted the same two-way ANCOVA when chlorpromazine equivalents of antipsychotics were also added as a covariate to control for effects of antipsychotics on task scores in patients diagnosed with schizophrenia (n=23 due to missing medication data in five patients). Results, similar to those of the two-way ANCOVA without chlorpromazine equivalents of antipsychotics as a covariate, showed no interaction (P=0.626) and no task effect (F[1,18]=2.33; P=0.144; η^2=0.12). RAS effects remained significant (F[2,36]=4.19; P=0.023; η^2=0.19). Results of post hoc tests with the Bonferroni correction were similar to those of the two-way ANCOVA without chlorpromazine equivalents of antipsychotics as a covariate.

Discussion

This study showed that patients with schizophrenia spectrum disorders had impaired unimanual and bimanual movement speed. In addition, RAS with a faster tempo induced faster upper-limb movements, including unimanual and bimanual movements, in patients and psychiatrically healthy people, showing that the use of RAS may be effective in regulating upper-limb movement speed.

Patients with schizophrenia spectrum disorders showed impaired unimanual and bimanual movement speed, which is consistent with earlier literature [23,24,31]. It has been suggested that the existence of motor problems in patients may be jointly explained by schizophrenia itself and possible motor side-effects of antipsychotics [6,7], both of which are associated with aberrant or disrupted neural activities in basal ganglia [7-9,32]. In addition, aberrant movements in patients are also linked to dysfunctional cerebellum [10-12]. It has been known that basal ganglia and cerebellum are responsible for regulating motor signals from the cortical regions and transmitting the integrated signals

back to the cortex so that movements could be executed efficiently [8,33-36]. It is reasonable that once basal ganglia or cerebellum is impaired, disorganized motor signals result in slow execution of movements.

The results showed that RAS with a faster tempo induced faster upper-limb movements in participants, including patients with schizophrenia spectrum disorders, which corresponds with earlier studies [16,18,19] indicating positive effects of RAS on movement speed in populations with aberrant basal ganglia. This study extends earlier findings by showing that upper-limb movements also responded to RAS as well as that RAS was also effective for patients with schizophrenia spectrum disorders. The profound effects of RAS on movement speed have been explained by the auditory-motor entrainment [17,18,20], which means innate synchronization of movement rhythm to the regular beat of music/sounds [17,18,20]. Because of this auditory-motor coupling, RAS is able to provide the timing template for movements and regulate movement speed [17,18,20]. One neural basis for the auditory-motor entrainment is rich neural connections between auditory and motor brain areas in a subcortical level (e.g., through the cerebello-cortical neural network) and a cortical level (e.g., direct neural connections between auditory and motor brain regions) in humans [20]. Neuroimaging studies have reported that motor cortices are active when people only listen to rhythmic sounds without requirements of doing a movement task [37,38], and that the firing pattern of the motor neurons and that of auditory neurons activated by RAS are coupled [39], supporting the auditory-motor entrainment. In earlier studies examining patients with impaired basal ganglia, such as those with Parkinson's disease [18,20], explanations for auditory-motor entrainment and thus positive effects of RAS on movement speed particularly involved the cerebellum. It has been reported [18,20] that the cerebellar-cortical network is activated when movements are guided by RAS from the environment, whereas basal ganglia-thalamo-cortical circuits are closely linked to self-paced movements. Given differential neural pathways between externally-guided movements versus internally driven movements [18,20], RAS is effective in regulating movement speed in patients with Parkinson's disease. However, it is noteworthy that neural connections between auditory and motor brain areas underpinning auditory-motor entrainment are not simply the cerebello-cortical neural network [20]. Our findings showed that RAS was also effective in regulating movement speed in patients with schizophrenia spectrum disorders, who have been reported to have dysfunctional basal ganglia and cerebellum [8,12,13]. These results suggested that other neural pathways linking auditory and motor brain regions, such as direct neural routes in a cortical level [20], may be still functional in patients with schizophrenia spectrum disorders so as to keep auditory-motor entrainment work and enable positive effects of

faster RAS on movement speed. Taken together, RAS may involve alternative neural pathways to modulate movement speed [20] and thus to compensate for impaired function of basal ganglia and cerebellum in patients.

Compared with the baseline no-RAS situation, the normal RAS, which had the baseline no-RAS movement tempo, was found to induce slower upper-limb movements in patients. The results concerning upper-limb immediate responses to the presence of the normal RAS are inconsistent with previous findings [40,41], which mainly focused on immediate responses in gaits. Earlier studies have reported that although mixing the use of normal and fast RAS in the training does improve walking speed in patients with aberrant basal ganglia [18,20,42], manipulation of the normal RAS itself (presence versus the no-RAS situation) causes no effects on walking speed [40,41]. The differential influence of the normal RAS on upper-limb movements and gaits may be due to a difference in task difficulty. It has been indicated that more difficult tasks [43,44] or those requiring modulation of more sensory inputs simultaneously [45] undermine effects of sensory stimulation on movements in patients with aberrant basal ganglia. Compared with walking, upper-limb object-directed movements rely more on visual information to correctly touch and place objects [46,47] and thus may demand more complicated sensory integration in patients once RAS is provided. In that case, it is possible that effects of the normal RAS, which are neutral on walking speed [40,41], become negative on upper-limb movement speed due to increased difficulty across tasks.

The findings of this study may be of clinical meaning. Our data indicating slow unimanual and bimanual movements in patients with schizophrenia spectrum disorders warrant clinical attention to developing tailor-made strategies to enhance patients' movements. In addition, when RAS is applied to movement therapy for patients, faster RAS may be beneficial to inducing faster upper-limb movements. Several issues need to be addressed in future studies. First, this study examined two RAS tempo speed. In future research, RAS with varying tempo speed could be further tested to determine the range of the RAS tempo speed that benefits upper-limb movements and to determine which RAS tempo speed, compared with the baseline no-RAS situation, starts to induce faster movements. Second, this study examined immediate effects of RAS on upper-limb movements. The next step is to investigate efficacy of long-term upper-limb movement training manipulating RAS in patients. Third, this study did not aim to and was unable to confirm that the presence of RAS with the fast tempo (120% of the baseline no-RAS movement tempo) did induce faster movements than did the absence of RAS. In this study, because the baseline movement pace needed to be measured first to ascertain the normal and fast speed of the RAS tempo for each participant, movements in response to RAS were always tested after baseline no-RAS movements. Therefore, this

normal experimental procedure led to a failure of ruling out a possible explanation that faster movements in the situation of the fast RAS compared with the baseline no-RAS were due to movement practice. Future research randomly assigning patients to two movement training groups, one of which has the aid of RAS and the other does not, will be of use to examine effects of the presence of RAS on upper-limb movements without confounding influences of practice. Fourth, this study did not collect data concerning illness duration after diagnosis, duration of untreated psychosis, onset age, severity of psychotic symptoms, severity of extrapyramidal symptoms, substance abuse, and smoking in patients, which should be collected in future studies to present complete background information in patients. In addition, future randomized controlled trials testing effects of long-term movement training using RAS in patients need to take these clinical and demographic characteristics in patients into account to prevent possible confounding influences on movements. Last, this study only targeted right-handed participants and collected right-hand and both-hand task data. Future research may collect right-hand and left-hand task data in participants, either right-handed or left-handed, to examine group differences and RAS effects on a hand laterality score.

Conclusions

The major contribution of this study is to demonstrate that upper-limb movements, including unimanual and bimanual movements, in patients with schizophrenia spectrum disorders and psychiatrically healthy people responded to changes in RAS. We found that faster RAS was effective in inducing faster upper-limb movements, which suggests that manipulating RAS may be a feasible therapeutic strategy utilized to regulate upper-limb movement speed in patients. Future research is suggested to further test effects of long-term movement training applying RAS on patients' movement speed.

Compliance with ethical standards

This study was performed in line with the principles of the Declaration of Helsinki. This study has been reviewed by the Institutional Ethics Review Board of Hong Kong Polytechnic University (the approval number: HSEARS20170419006). All participants were informed of the research procedure and signed the consent form before joining the study.

Funding source

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest

All authors declare that they have no conflict of interest.

Availability of data and material

Not applicable

Code availability

Not applicable

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Table 1 Characteristics of participants

	M±SD or n (%)		*P*-value
	Patients (n=30)	Psychiatrically healthy people (n=30)	
Age (years)	47.77±11.54	40.43±14.74	0.036
Education (years)	9.43±3.32	12.43±3.67	0.002
Male	17 (56.67)	15 (50.00)	0.605
Diagnosis			--
Schizophrenia	28 (93.33)	--	
Schizoaffective disorder	2 (6.67)	--	
Chlorpromazine equivalents (mg/day)[a]	537.83±417.84	--	--

[a]n=25 due to missing medication data of five patients diagnosed with schizophrenia

Table 2 Results of two-way analysis of covariance after controlling confounding effects of age, education, and the gender ratio on the right-hand task score and the both-hand task score in a total of 60 participants (30 patients and 30 psychiatrically healthy people)

	Descriptive data (M±SD)			Main effects	Post hoc tests for RAS conditions[a]
	1. Baseline	2. Normal RAS	3. Fast RAS		
Right-hand task					
Patients	11.66±1.78	10.95±1.56	12.28±1.93	Group: F[1,54]=56.05; P<0.001; η^2=0.51	1*vs.*2: P<0.001
Psychiatrically healthy people	15.06±1.61	14.71±1.68	16.07±1.97	RAS: F[2,108]=3.14; P=0.047; η^2=0.06	1*vs.*3: P<0.001 2*vs.*3: P<0.001
Both-hand task					
Patients	9.04±1.72	8.52±1.70	9.23±1.83	Group: F[1,54]=42.03; P<0.001; η^2=0.44	1*vs.*2: P<0.001
Psychiatrically healthy people	11.72±1.31	11.28±1.43	12.37±1.58	RAS: F[2,108]=4.55; P=0.013; η^2=0.08	1*vs.*3: P=0.023 2*vs.*3: P<0.001

RAS, rhythmic auditory stimulation

[a]*P*-values were adjusted using the Bonferroni method for multiple comparisons

Table 3 Results of three-way analysis of covariance after controlling confounding effects of age, education, and the gender ratio on the task score in a total of 58 participants (28 patients diagnosed with schizophrenia and 30 psychiatrically healthy people)

	Descriptive data (M±SD)			Main effects	Post hoc tests for RAS conditions[a]
	1. Baseline	2. Normal RAS	3. Fast RAS		
Right-hand task					
Patients	11.68±1.84	10.89±1.60	12.25±1.99		
Psychiatrically healthy people	15.06±1.61	14.71±1.68	16.07±1.97	Group: F[1,52]=57.11; P<0.001; η^2=0.52	1 *vs.* 2: P<0.001
				RAS: F[2,104]=4.53; P=0.013; η^2=0.08	1 *vs.* 3: P<0.001
Both-hand task				Task: F[1,52]=6.12; P=0.017; η^2=0.11	2 *vs.* 3: P<0.001
Patients	8.96±1.75	8.39±1.69	9.05±1.75		
Psychiatrically healthy people	11.72±1.31	11.28±1.43	12.37±1.58		

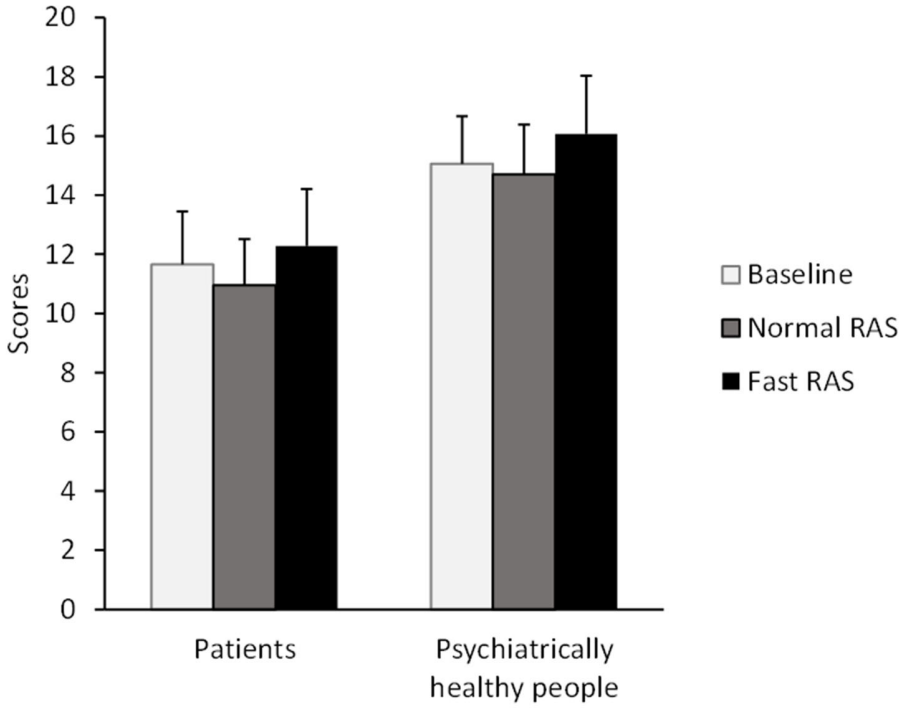
RAS, rhythmic auditory stimulation

[a]*P*-values were adjusted using the Bonferroni method for multiple comparisons

Figure captions

Fig. 1 Performance in the baseline, normal-RAS, and fast-RAS conditions for patients with schizophrenia spectrum disorders (n=30) and psychiatrically healthy people (n=30). (A) The right-hand task performance. (B) The both-hand task performance. RAS, rhythmic auditory stimulation. Error bars represent one standard deviation

A. Right-hand task



B. Both-hand task